# EXHIBIT 6

DRUGDEX-EV 1728

MICROMEDEX
DRUGDEX® Evaluations

Database updated February 2007

**OLANZAPINE**



**0.0 Overview**

**1)** Class
**a)** This drug is a member of the following class(es):
Antipsychotic
Thienobenzodiazepine
**2)** Dosing Information
**a)** Adult
**1)** Agitation - Bipolar I disorder - Mania
**a)** initial, 10 mg INTRAMUSCULARLY; lower dose of 5 mg or 7.5 mg may be used if indicated. Usual effective dosage range is 2.5 mg to 10 mg
**b)** subsequent doses may be given INTRAMUSCULARLY in doses up to 10 mg. Maximal dosing, three 10 mg doses given 2 to 4 hours apart (monitor for orthostatic hypotension prior to the administration of repeated doses)
**2)** Agitation - Schizophrenia
**a)** initial, 10 mg INTRAMUSCULARLY; lower dose of 5 mg or 7.5 mg may be used if indicated. Usual effective dosage range is 2.5 mg to 10 mg
**b)** subsequent doses may be given INTRAMUSCULARLY in doses up to 10 mg. Maximal dosing, three 10 mg doses given 2 to 4 hours apart (monitor for orthostatic hypotension prior to the administration of repeated doses)
**3)** Bipolar disorder, acute, Mixed or manic with or without psychotic features
**a)** (monotherapy) 10-15 mg ORALLY once a day; may increase/decrease dosage by 5 mg/day at intervals of at least 1 day. Usual effective dosage range is 5-20 mg/day; the safety of doses above 20 mg/day has not been evaluated in clinical trials
**4)** Bipolar disorder, acute - Bipolar disorder, manic episode
**a)** (in combination with lithium or valproate) 10 mg ORALLY once a day; usual effective dosage range is 5-20 mg/day; the safety of doses above 20 mg/day has not been evaluated in clinical trials
**5)** Bipolar disorder, Maintenance
**a)** (monotherapy) 5 to 20 mg ORALLY per day (after achieving a responder status for an average duration of two weeks)
**6)** Schizophrenia
**a)** 5-10 mg ORALLY once a day (target dose of 10 mg/day within several days); may increase/decrease

dosage by 5 mg/day at intervals of at least 1 week. Usual effective dosage range is 10-15 mg/day; the safety of doses above 20 mg/day has not been evaluated in clinical trials

**b)** Pediatric

**1)** safety and effectiveness in pediatric patients have not been established

**3)** Contraindications

**a)** hypersensitivity to olanzapine products

**4)** Serious Adverse Effects

**a)** Tardive dyskinesia

**b)** Water intoxication syndrome

**5)** Clinical Applications

**a)** FDA Approved Indications

**1)** Agitation - Bipolar I disorder - Mania

**2)** Agitation - Schizophrenia

**3)** Bipolar disorder, acute, Mixed or manic with or without psychotic features

**4)** Bipolar disorder, acute - Bipolar disorder, manic episode

**5)** Bipolar disorder, Maintenance

**6)** Schizophrenia

## 1.0 Dosing Information



### 1.1 Drug Properties

**A)** Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

**B)** Synonyms

Olanzapine

**C)** Physicochemical Properties

**1)** Molecular Weight

**a)** 312.44 (Prod Info Zyprexa(R), 2004)

**2)** Solubility

**a)** Practically insoluble in water (Prod Info Zyprexa(R), 2004)

### 1.2 Storage and Stability

**A)** Oral route

**1)** Store at controlled room temperature, 20 to 25 degrees C (68 to 77 degrees F) (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a). Protect from light and moisture

**B)** Extemporaneous Formulation - Oral route

**1)** Olanzapine is practically insoluble in water. A 1-milligram per milliliter (mg/mL) suspension prepared from crushed tablets in a pediatric mixture base (containing syrup, carboxymethylcellulose and parabens) was found to be stable for 14 days when stored in a refrigerator and protected from light (Harvey et al, 2000). Care in preparation and administration is advised as olanzapine may be irritating to the eye and can cause contact dermatitis. When breaking or crushing olanzapine tablets it is recommended to wear gloves and wash hands before and after exposure (Personal Communication, 2001).

### 1.3 Adult Dosage

### 1.3.1 Normal Dosage

#### 1.3.1.A Intramuscular route

##### 1.3.1.A.1 Agitation - Manic bipolar I disorder - Schizophrenia

**a)** The recommended intramuscular dose for the treatment of AGITATION ASSOCIATED WITH SCHIZOPHRENIA OR BIPOLAR MANIA is 10 milligrams (mg). A lower dose of 5 mg or 7.5 mg may be used when clinically indicated. Efficacy of intramuscular olanzapine has been demonstrated in a dosage range of 2.5 mg to 10 mg (Prod Info Zyprexa(R) IntraMuscular, 2004).
**b)** The efficacy of repeated doses of intramuscular olanzapine in agitated patients has not been evaluated in controlled clinical trials. However, if agitation persists after the initial dose and additional intramuscular doses are warranted, subsequent doses up to 10 milligrams (mg) may be given. The safety of total daily doses greater than 30 mg, or 10 mg injections given more frequently than 2 hours after the initial dose, and 4 hours after the second dose have not been evaluated in clinical trials. Maximal dosing of intramuscular olanzapine (ie, three 10 mg doses administered 2 to 4 hours apart) may be associated with an increased risk of orthostatic hypotension. It is recommended that patients requiring subsequent intramuscular injections be assessed for orthostatic hypotension prior to the administration of any subsequent doses of intramuscular olanzapine for injection. Additional doses should not be administered to a patient with a clinically significant postural change in systolic blood pressure. If ongoing olanzapine therapy is necessary, oral olanzapine may be initiated in a range of 5 to 20 mg/day as soon as clinically appropriate (Prod Info Zyprexa(R) IntraMuscular, 2004).
**c)** Intramuscular olanzapine for injection is intended for intramuscular use only; do NOT administer intravenously or subcutaneously. Inject slowly, deep into the muscle mass (Prod Info Zyprexa(R) IntraMuscular, 2004).

#### 1.3.1.B Oral route

##### 1.3.1.B.1 Agitation - Manic bipolar I disorder - Schizophrenia

**a)** In one study, rapid initial dose escalation of oral olanzapine was effective in the treatment of acute agitation in patients with schizophrenia or bipolar disorder. Investigators used a dosing regimen of 20 to 40 milligrams (mg)/day for 2 days, then 20 to 30 mg/day for 2 days, and then 5 to 20 mg/day for 3 days. Also effective was the more conventional dosing regimen of olanzapine 10 mg daily with adjunctive lorazepam as needed for 4 days, and then olanzapine 5 to 20 milligrams for 3 days (Baker et al, 2003).

##### 1.3.1.B.2 Bipolar disorder, Maintenance

**a)** MONOTHERAPY
**1)** Bipolar patients responding to initial olanzapine therapy for an average period of two weeks have been successfully maintained on olanzapine monotherapy at a dose of 5 to 20 milligrams/day. The long-term usefulness of olanzapine for the individual patient should be periodically re-evaluated if olanzapine is used for extended periods of time (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).

##### 1.3.1.B.3 Bipolar disorder, manic episode

**a)** MONOTHERAPY
**1)** In clinical trials evaluating the short-term (3 to 4 weeks) effects of olanzapine in acute mania, efficacy was observed with doses of 5 milligrams (mg) to 20 mg daily. The recommended initial

dosage of olanzapine is 10 or 15 milligrams (mg) once daily and doses may be increased, at intervals of not less than 24 hours, by 5 mg daily. Doses above 20 mg/day have not been evaluated for safety in clinical trials (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).

**b)** COMBINATION THERAPY

**1)** In clinical trials evaluating the short-term (6 weeks) effects of olanzapine in acute mania, efficacy was observed with doses of 5 to 20 milligrams (mg) daily. The recommended initial dosage of olanzapine in combination with lithium or valproate is 10 mg once daily. Doses above 20 mg/day have not been evaluated for safety in clinical trials (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).

**1.3.1.B.4 Schizophrenia**

**a)** Initial dosages are 5 to 10 milligrams administered on a once-a-day schedule without regard to meals. A target dosage of 10 milligrams/day within several days of initiation of therapy is recommended. If dosage adjustments are needed, decrease or increase the dosage by 5 milligrams/day. Dosage adjustments should typically occur at intervals of not less than 1 week (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).

**b)** In clinical trials, antipsychotic efficacy occurred at a dosage range of 10 to 15 milligrams/day. Doses above 10 milligrams/day were not demonstrated to be more efficacious than the 10 milligrams/day dose. The safety of doses above 20 milligrams/day has not been evaluated in clinical trials (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).

**c)** Effective doses of olanzapine in the treatment of schizophrenia have ranged from 7.5 to 40 milligrams daily (Alao, 1999)(Nemeroff, 1997a); (Beasley et al, 1996)(Beasley et al, 1996aa; Anon, 1994b; Anon, 1994aa). Clinical trials have shown that 10 milligrams/day is a therapeutic dose. The 15-milligram dose may have greater efficacy in relieving negative symptoms; further studies are needed (Nemeroff, 1997a).

**1.3.1.C Parkinson's disease - Psychotic disorder**

See Drug Consult reference: THERAPY OF PSYCHOTIC DISTURBANCES IN PARKINSONIAN PATIENTS

**1.3.1.D Trichotillomania**

See Drug Consult reference: TRICHOTILLOMANIA - DRUG THERAPY

**1.3.1.E)** ORAL DISINTEGRATING TABLETS - PATIENT INSTRUCTIONS

**1)** For administration of oral disintegrating tablets, peel back foil on blister pack to expose tablet; do NOT push the tablet through the foil backing. Use dry hands to remove the tablet from the blister unit and immediately place the entire tablet in the mouth. Tablets disintegrate rapidly in saliva and can be swallowed with or without liquid (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).

**1.3.1.F)** INTRAMUSCULAR SOLUTION PREPARATION

**1)** For the preparation of solution for intramuscular injection containing approximately 5 milligrams/milliliter (mg/mL) of olanzapine, dissolve the contents of the supplied vial using 2.1 mL of Sterile Water for Injection. The resulting solution should appear clear and yellow. Olanzapine solution should be used immediately (within 1 hour) after reconstitution and any unused portion should be discarded. The following table provides injection volumes for delivering various doses of intramuscular olanzapine for injection reconstituted with Sterile Water for Injection (Prod Info Zyprexa(R) IntraMuscular, 2004):

Dose (mg)

Volume of Injection (mL)
10.0
Withdraw total contents of vial
7.5
1.5
5.0
1.0
2.5
0.5

**1.3.1.G)** SWITCHING TO OLANZAPINE

**1)** Schizophrenic and schizophreniform patients may be successfully transitioned from clozapine to olanzapine by adding olanzapine 5 milligrams (mg) daily to a stable dose of clozapine (Henderson et al, 1998). Olanzapine is increased by 2.5 to 5 mg weekly to a maximum of 30 mg/day. After the first week, clozapine doses should be gradually decreased by increments of 25 to 50 mg per week.

**2)** Switching patients to olanzapine from conventional antipsychotic therapy or risperidone was most successful when olanzapine was immediately implemented at the full therapeutic dose and other antipsychotics were gradually discontinued. In a study of 209 clinically stable outpatients diagnosed with schizophrenia or schizoaffective disorder, 4 treatment strategies were used. Patients were randomized to undergo abrupt or gradual discontinuation of their prior antipsychotic drug and immediate or stepwise initiation of olanzapine. Olanzapine was administered in doses of 10 milligrams (mg) daily (QD) for 3 weeks or in a stepwise fashion (1 week of placebo, followed by 1 week of olanzapine 5 mg QD and then 1 week of olanzapine 10 mg). The efficacy of each strategy was assessed using the Clinical Global Impressions (CGI) Improvement scale, Patient's Global Impressions (PGI) improvement scale and Positive and Negative Syndrome Scale (PNSS). These scoring systems showed that immediate initiation of olanzapine with gradual discontinuation of the original drug therapy was the safest and most effective approach. However, all strategies were effective; by week 3, the majority of patients on all regimens had either improved or were clinically unchanged without increased risk of relapse or of drug withdrawal symptoms. Patients who abruptly discontinued antipsychotic medication and gradually implemented olanzapine had a significantly greater incidence of sleep disorders than those using other strategies. Drowsiness occurred significantly more often in when antipsychotic medication was abruptly discontinued with immediate implementation of olanzapine therapy than with other approaches (Kinon et al, 2000).

### 1.3.2 Dosage in Renal Failure

**A)** Patients with renal impairment DO NOT require a dosage adjustment. The pharmacokinetic parameters were similar between patients with severe renal impairment and normal patients. Only 7% of olanzapine is excreted in the urine as unchanged drug (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b). However, a lower initial dose of 5 milligrams daily should be considered (Prod Info Zyprexa(R), 1998).

### 1.3.3 Dosage in Hepatic Insufficiency

**A)** Olanzapine is extensively metabolized, however, no change in dosage is needed. In patients with significant liver function impairment (Childs Pugh Classification A and B), little effect was seen on the pharmacokinetics of olanzapine (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).

### 1.3.4 Dosage in Geriatric Patients

**A)** Caution should be used when oral olanzapine is administered to the elderly, especially if there are other factors that may influence drug metabolism and/or pharmacodynamic parameters (Prod Info Zyprexa(R),

Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).
**B)** The recommended intramuscular dose for elderly patients is 5 milligrams per injection (Prod Info Zyprexa(R) IntraMuscular, 2004).

### 1.3.5 Dosage Adjustment During Dialysis

**A)** HEMODIALYSIS
**1)** Olanzapine is not removed by dialysis (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).
**B)** PERITONEAL DIALYSIS
**1)** Olanzapine is not removed by dialysis (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).

### 1.3.6 Dosage in Other Disease States

**A)** SPECIAL POPULATIONS
**1)** The recommended starting oral dose is 5 milligrams in the following populations: patients who are debilitated, who have a predisposition to hypotensive reactions, who exhibit a combination of factors that may cause a slower metabolism of olanzapine (eg, nonsmoking females 65 or older) or who may be pharmacodynamically sensitive to olanzapine (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).
**2)** The recommended intramuscular dose is 2.5 milligrams per injection for patients who are debilitated, have a predisposition to hypotensive reactions, or may be pharmacodynamically sensitive to olanzapine (Prod Info Zyprexa(R) IntraMuscular, 2004).
**3)** No dosage modification is needed but the manufacturer reports that the clearance of olanzapine is 30% lower in females (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).
**4)** No dosage modification is needed but the manufacturer reports that the clearance of olanzapine is 40% higher in smokers than in nonsmokers (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).
**5)** The combined effects of age, smoking, and gender could cause substantial pharmacokinetic differences in populations. For example the clearance in young male smokers may be 3 times higher than that in elderly nonsmoking females (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b). Age over 65, gender, or smoking status alone does NOT require dosage modification.

## 1.4 Pediatric Dosage

### 1.4.1 Normal Dosage

#### 1.4.1.A Anorexia nervosa

See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

## 2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels
ADME

**2.1 Onset and Duration**

**A)** Onset
**1)** Initial Response
**a)** Schizophrenia: 1 week (Beasley et al, 1996).

**2.2 Drug Concentration Levels**

**A)** Therapeutic Drug Concentration
**1)** Schizophrenia, greater than 9 ng/ml (Perry et al, 1997).
**a)** In acutely schizophrenic patients receiving olanzapine (n=79), 45% of patients with a trough level above 9.3 ng/ml responded after 6 weeks of therapy versus only 15% of patients with concentrations less than 9.3 ng/ml responding (Perry et al, 1997).
**B)** Time to Peak Concentration
**1)** Oral: 6 hours (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004). Oral: 6 hours (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004).
**a)** In an open-label, inpatient trial involving 8 patients (ages 10 to 18 years) receiving olanzapine 2.5 to 20 milligrams daily for 8 weeks, the mean maximum plasma concentration was 115.6 +/- 26.7 nanograms/milliliter. The mean time to maximum concentration was 4.7 +/- 3.7 hours. The concentrations among these adolescent patients are similar to the concentrations observed in nonsmoking adult patients being treated with olanzapine for schizophrenia, but nearly twice the average concentrations in smokers (Grothe et al, 2000).
**2)** Intramuscular: 15 to 45 minutes (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004).

**2.3 ADME**

**2.3.1 Absorption**

**A)** Bioavailability
**1)** Oral: Well-absorbed (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004).
**a)** Extensively eliminated by first-pass metabolism; 40% of dose metabolized before reaching systemic circulation (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004; Bever & Perry, 1998a).
**B)** Effects of Food
**1)** None (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004).

**2.3.2 Distribution**

**A)** Distribution Sites
**1)** Protein Binding
**a)** 93% (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004).
**1)** The primary binding sites are albumin and alpha-1- acid glycoprotein (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004).
**B)** Distribution Kinetics
**1)** Volume of Distribution
**a)** 1000 L (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004).

**2.3.3 Metabolism**

**A)** Metabolism Sites and Kinetics

**1)** Liver, extensively metabolized (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004; Anon, 1994).

**a)** The primary metabolic pathways for olanzapine are direct glucuronidation and oxidation mediated by CYP1A2, CYP2D6, and the flavin-containing monooxigenase system. CYP2D6 appears to be a minor pathway (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004).

**b)** Forty percent is metabolized via first pass metabolism (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004).

**B)** Metabolites

**1)** 10-N-glucuronide, (inactive) (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004).

**2)** 4'-N-desmethyl olanzapine, (inactive) (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004).

**2.3.4 Excretion**

**A)** Kidney

**1)** Renal Excretion (%)

**a)** 57% (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004; Anon, 1994).

**B)** Total Body Clearance

**1)** 26.1 L/hr (Kando, 1997).

**a)** Clearance ranges from 12 to 47 L/hour (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004).

**b)** In 8 pediatric and adolescent patients (ages 10 to 18 years) receiving 2.5 to 20 milligrams olanzapine daily for 8 weeks, the mean plasma clearance was 9.6 +/- 2.4 liters/hour (Grothe et al, 2000).

**C)** Other

**1)** OTHER EXCRETION

**a)** Feces, 30% (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004; Anon, 1994).

**2.3.5 Elimination Half-life**

**A)** Parent Compound

**1)** ELIMINATION HALF-LIFE

**a)** 21 to 54 hours (mean = 30 hours) (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004; Anon, 1994).

**1)** In 8 pediatric and adolescent patients (ages 10 to 18 years) receiving 2.5 to 20 milligrams olanzapine daily for 8 weeks, the mean elimination half-life was 37.2 +/- 5.1 hours (Grothe et al, 2000).

**2)** Although the mean elimination half-life of olanzapine is prolonged in the elderly (young patients: 33.8 hours vs. 65 years and older: 51.8 hours) and renal clearance is reduced from 18.2 Liters/hour (L/h) in the young to 17.5 L/h in those 65 years and older, pharmacokinetic variability is not greater than in young patients. Thus, a dose reduction is not necessary in otherwise healthy elderly patients (Prod Info Zyprexa(R), 1998a).

**3.0 Cautions**

Contraindications
Precautions
Adverse Reactions
Teratogenicity/Effects in Pregnancy/Breastfeeding
Drug Interactions

**3.0.A)** Black Box WARNING

**1)** Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 times to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Olanzapine is not approved for the treatment of patients with dementia-related psychosis (Prod Info ZYPREXA(R), ZYPREXA ZYDIS(R), ZYPREXA IntraMuscular(R), 2005).

**3.1 Contraindications**

**A)** hypersensitivity to olanzapine products

**3.2 Precautions**

**A)** diabetes mellitus
**B)** elderly patients with **dementia** (unapproved use); increased risk of death (1.6 to 1.7 times greater than placebo) reported when atypical antipsychotics were used off-label to treat behavorial disorders associated with **dementia**; most deaths were attributed to cardiovascular events (eg, heart failure or sudden death) or infections (mostly pneumonia) (Prod Info ZYPREXA(R), ZYPREXA ZYDIS(R), ZYPREXA IntraMuscular(R), 2005)
**C)** elderly patients with dementia-related psychosis; increased risk of cerebrovascular adverse events (ie, stroke, transient ischemic attack) including death
**D)** history of breast cancer
**E)** history of neuroleptic malignant syndrome
**F)** hyperglycemia
**G)** patients at risk for aspiration pneumonia
**H)** patients who experience conditions that may contribute to an elevation in core body temperature
**I)** patients at risk for suicide
**J)** patients with liver disease
**K)** patients with significant prostatic hypertrophy, narrow angle glaucoma, or history of paralytic ileus
**L)** patients with cardiovascular disease, cerebrovascular disease, or conditions that would predispose patients to hypotension
**M)** seizure disorder or conditions that could lower seizure threshold
**N)** signs and symptoms of tardive dyskinesia

**3.3 Adverse Reactions**

**3.3.1 Cardiovascular Effects**

**3.3.1.A Cardiovascular finding**

**1)** Summary

**a)** The manufacturer reports that POSTURAL HYPOTENSION (3-5%), TACHYCARDIA (3%),

HYPERTENSION (2%), CHEST PAIN (3%), and PERIPHERAL EDEMA (3%) have occurred with olanzapine therapy (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a). Caution is recommended when using olanzapine concurrently with drugs that prolong the QT interval (Prod Info Zyprexa(R), 1998). A case of HYPOTENSION and BRADYCARDIA has been reported (Markowitz et al, 2002).

**2)** Postural hypotension, tachycardia, hypertension, chest pain, and peripheral edema are reported with olanzapine administration. Caution is recommended when using olanzapine concomitantly with drugs that prolong the QT interval.

**3)** LITERATURE REPORTS

**a)** A 24-year-old, healthy, non-smoking, woman volunteer experienced hypotension (70/30 mmHg) and bradycardia (pulse 30) one and a half to 2 hours after taking a single oral dose of olanzapine 5 milligrams (mg). Lying down with feet elevated brought both pulse and blood pressure back to her normal values within 20 minutes. The maximum plasma concentration of olanzapine in this subject (13 nanograms/milliliter) was unusually high and occurred earlier (at 3 hours) than the generally reported range for tmax (5 to 6 hours). Her Cmax was in the range expected for a single dose of 10 to 15 mg of olanzapine (Markowitz et al, 2002).

**b)** Unlike other antipsychotic medications, olanzapine does NOT contribute significantly to QTc prolongation that could result in potentially severe ventricular dysrhythmias, due to its mechanism of action (Czekalla et al, 2001; Isbister et al, 2001).

**c)** Although olanzapine has not been associated with sustained QT-interval prolongation, caution is recommended during concomitant treatment with drugs that do prolong the QT-interval, especially in the elderly. In a study of 1685 subjects, only 8 experienced multiple QT-interval prolongations (Prod Info Zyprexa(R), 1998).

**d)** Small reductions in orthostatic blood pressure have been reported in olanzapine-treated patients during clinical trials (Beasley et al, 1996)(Beasley et al, 1996a).

**e)** Tachycardia occurred in greater than 5% of patients in clinical trials, with an overall mean increase in heart rate of 2.4 beats/minute (Prod Info Zyprexa(R), 1996). Chest pain has also been reported in clinical trials.

### 3.3.1.B Orthostatic hypotension

**1)** Summary

**a)** ORTHOSTATIC HYPOTENSION has been observed in greater than 5% of patients participating in olanzapine clinical trials . A mean increase in heart rate of 2.4 beats per minute has been reported in clinical trials with TACHYCARDIA occurring in greater than 5% of the patients. It is possible that this effect is associated with orthostatic hypotensive changes (Bronson & Lindenmayer, 2000; Prod Info Zyprexa(R), 1996). Slight reductions in orthostatic blood pressure have been reported in olanzapine-treated patients (Beasley et al, 1996), although this is of doubtful clinical relevance. Heart rate has not been affected (Beasley et al, 1996).

**2)** Incidence: 2-3%

## 3.3.2 Dermatologic Effects

### 3.3.2.A Dermatological finding

**1)** Summary

**a)** A 36-year-old African-American man developed a PUSTULAR SKIN ERUPTION 2 weeks after beginning olanzapine therapy. Pustular lesions initially began on his face and spread to his hips and buttocks. One day later he developed ERYTHEMATOUS PLAQUES on his neck, hips and buttocks. He had no lymphadenopathy or fever. Olanzapine was discontinued and warm compresses were applied. The eruptions resolved within 1 week (Adams & Mutasim, 1999).

**2)** Pustular eruptions, sweating and erythematous plaques are reported with olanzapine administration.

**3.3.2.B Sweating symptom**

**1)** Summary

**a)** The manufacturer reports that sweating has been associated with olanzapine therapy (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a).

**3.3.3 Endocrine/Metabolic Effects**

**3.3.3.A Body temperature finding**

**1)** Summary

**a)** HYPOTHERMIA developed in a 54-year-old hemodialysis patient with end- stage renal disease following the use of olanzapine. The man initially received a 21-day course of oral olanzapine 2.5 milligrams (mg) daily for the treatment of sudden-onset night delirium with visual hallucinations and abnormal behaviors. The symptoms of delirium resolved, but then reappeared 7 days later. He was given olanzapine again at the same dose for 10 days; however, following the first dose of medication, his body temperature suddenly decreased to less than 34 degrees Celsius. Hypothermia persisted from day 2 of the 10-day olanzapine administration, and did not resolve until 6 days after olanzapine was discontinued (Fukunishi et al, 2003).

**b)** Disruption of the body's ability to reduce core body temperature may occur with antipsychotic agents. ELEVATED BODY TEMPERATURE has been reported following therapeutic doses in clinical trials (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a). Patients experiencing conditions that may contribute to an ELEVATED CORE BODY TEMPERATURE (eg exercising strenuously, exposure to extreme heat, or dehydration) should use appropriate care (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a).

**2)** Elevated body temperature, hypothermia, and neuroleptic malignant syndrome (NMS) are reported with olanzapine administration.

**3.3.3.B Diabetes mellitus**

**1)** Summary

**a)** New onset diabetes mellitus (DM) and DIABETIC KETOACIDOSIS have been reported with the administration of olanzapine. At least 25 fatalities have been reported in association with olanzapine-induced diabetic ketoacidosis (Torry & Swalwell, 2003)(Goldstein et al, 1999; Lindenmayer & Patel, 1999; Gatta et al, 1999).

**2)** LITERATURE REPORTS

**a)** A 51-year-old woman with schizoaffective disorder and type 2 diabetes (stabilized on metformin 1 gram twice daily and gliclazide 160 mg twice daily) developed hyperglycemia, without weight gain, when an episode of elevated mood and psychosis was treated with olanzapine. She was initially treated with risperidone for 4 weeks but did not respond. Chlorpromazine also was not effective. Olanzapine, titrated to 30 milligrams at night) brought full remission of psychotic symptoms. Her blood glucose then began to increase, although her diet was controlled by the hospital. Oral hypoglycemic medications were increased to the maximum and she was started on actrapid insulin. Glucose levels remained unstable until olanzapine was tapered and discontinued, at which time her hypoglycemic medications were reduced to previous levels and actrapid insulin was discontinued. Zuclopenthixol was subsequently used to treat her schizoaffective disorder. The patient showed no significant weight gain during treatment with olanzapine, which suggests that olanzapine can have a direct effect on glucose regulation (Ramankutty, 2002).

**b)** A 27-year-old man developed signs of diabetes mellitus (polydipsia, polyphagia, nausea and vomiting, hyperglycemia, ketonuria) 2 years after starting olanzapine for treatment of schizophrenia.

He was treated with insulin, and his dose of olanzapine was increased from 10 milligrams/day (mg/day) to 15 mg/day to replace valproic acid, which he had taken for 3 years. After 3 months, insulin therapy was replaced by pioglitazone 30 mg/day, resulting in relatively good glycemic control. Olanzapine therapy was not discontinued because of the risk of psychotic worsening (Seaburg et al, 2001).

**c)** A 45-year-old obese man developed elevated fasting glucose 1 year after his treatment for schizophrenia was changed from risperidone to olanzapine (20 to 25 milligrams/day (mg/day)). Six months later, he was treated with glyburide 1.25 mg/day. Over the next 6 months, his glycosylated hemoglobin levels remained stable, but his weight began to increase. Five months later, he complained of diarrhea and weight loss. His glyburide dose was increased to 1.88 mg/day. With further symptoms (polyuria, polydipsia, and diaphoresis), his glyburide dosage was increased to 10 mg twice daily, insulin treatment was started, and olanzapine was replaced by risperidone. Six weeks after discontinuation of olanzapine, the patient's glycosylated hemoglobin had dropped to 6%. Insulin was discontinued, glyburide was reduced to 1.25 mg/day, and his weight stabilized. Five months later, his diabetes was well controlled (Bechara et al, 2001).

**d)** Olanzapine-induced GLUCOSE DYSREGULATION has been reported as an adverse effect, possibly due to drug-induced weight gain. Olanzapine was associated with a severe exacerbation of type 2 diabetes in a 51-year-old woman with a major depressive disorder and substance abuse. Initially, the patient was treated with sertraline and haloperidol decanoate. After 4 weeks, sertraline was replaced by fluoxetine due to continued severe depressive symptoms. At week 18, haloperidol was replaced by olanzapine due to persistent auditory and visual hallucinations. Prior to initiation of olanzapine therapy, the patient's diabetes was well controlled by diet (glycosylated hemoglobin 6.5%, baseline fasting blood glucose 89 to 132 milligrams per deciliter (mg/dL). Twelve days after olanzapine was begun, glucose control diminished and continued to worsen despite treatment with glipizide, metformin, and diet. At week 26, fluoxetine therapy was replaced by venlafaxine due to inadequate antidepressant response. At week 35 (fasting blood glucose 120 to 461 mg/dL, glycosylated hemoglobin 12.5%), insulin therapy (NPH 70/30) was initiated and titrated to 70 units per day. Olanzapine was tapered during weeks 39 and 40 and discontinued. Two weeks after all antipsychotic therapy was stopped, the patient's fasting blood glucose levels had decreased to within 85 and 163 mg/dL. By the time of discharge, the insulin dose had been reduced to 45 units/day NPH 70/30 (Bettinger, 2000).

**e)** Diabetic ketoacidosis following 3 months of olanzapine therapy was reported in a 31-year-old man with no familial or personal history of diabetes. The patient was started on insulin and olanzapine was discontinued. Fifteen days later his insulin requirements decreased and then stopped. Eight months later the patient has remained metabolically stable, free of diabetic symptoms (Gatta et al, 1999).

**f)** Cases of new-onset diabetes mellitus (DM) were reported that developed after initiation of olanzapine treatment. The DM began between 5 weeks and 17 months (mean 26 weeks; median 20 weeks) after olanzapine initiation. Two cases presented with diabetic ketoacidosis. Four patients had a family history of DM and 4 patients experienced weight gain while on olanzapine. Olanzapine was eventually discontinued in all cases but in 4 out of 7 cases, medical treatment for DM was still required (Goldstein et al, 1999).

**g)** A 50-year-old African American man developed diabetic ketoacidosis after receiving 8 months of olanzapine therapy. At the time, he was receiving olanzapine 30 milligrams (mg) daily with divalproex 750 mg twice daily. He began insulin therapy but after the olanzapine was discontinued, his blood sugar returned to normal (Lindenmayer & Patel, 1999).

**h)** A 39-year-old man developed diabetic ketoacidosis after receiving olanzapine 10 milligrams (mg) for a treatment-refractory disorder. He had no family history or previous laboratory evidence of diabetes. His body mass index was high at 40 kilograms/meter(2) (kg/m(2)). He was admitted with asthenia, polyuria, dehydration, severe hyperglycemia [6 millimoles/liter (mmol/L)], and acidosis. His HbA(1c) was 14.7%. He was maintained on insulin 3 times daily. When olanzapine was discontinued, insulin requirements decreased after 15 days. His blood glucose and HbA(1c) became normal (Gatta et al, 1999).

### 3.3.3.C Endocrine finding

**1)** Diabetes mellitus (DM) and elevations in serum prolactin have been reported with olanzapine administration. Pancreatitis has been reported with the administration of olanzapine.

### 3.3.3.D Hyperglycemia

**1)** Summary

**a)** A 15-year-old African American boy developed hyperglycemia, along with weight gain and hypertriglyceridemia, while being treated with olanzapine for behavior disorders. At baseline, when the boy had been taking olanzapine for 3 months and valproic acid for over 12 months, all laboratory values were within normal ranges. His body mass index (BMI) was 28.7 kilograms per meter squared (kg/m(2)). Four months later, buspirone was added to his treatment. Within 2 months, his BMI had increased to 34.1 kg/m(2). Three months later, he had experienced weight loss (BMI=27.5 kg/m(2)) and developed polyuria and polydipsia. Fasting blood glucose was 368 milligrams/deciliter. Olanzapine was discontinued. Without hypoglycemic drugs, insulin treatment, or dietary changes, his serum glucose level normalized over the next 8 weeks, as did his serum triglyceride and cholesterol levels. Twenty weeks after the discontinuation of olanzapine, his BMI was 26.5 kg/m(2) (Domon & Webber, 2001).

### 3.3.3.E Hypoglycemia

**1)** Summary

**a)** HYPOGLYCEMIC COMA was reported in a frail, 95-year-old woman following olanzapine administration for the treatment of nocturnal psychomotor agitation associated with Alzheimer's **dementia**. Three days after the initiation of olanzapine at a dose of 2.5 milligrams daily, the woman was pale and sweaty; she appeared sleepy and could not be woken by verbal or tactile stimulation. She was treated with 33% glucose and recovered within approximately 20 minutes, however, hypoglycemia was noted again the following day. Olanzapine was withdrawn and the blood glucose profile stabilized two days later with the ongoing administration of 33% glucose. A direct cause and effect correlation could not be established because the patient had also been receiving enalapril, which has been documented to possibly induce hypoglycemia. While, a drug interaction between enalapril and olanzapine could not be ruled out, the authors did not feel that there was a correlation between enalapril and hypoglycemia because the patient had been receiving enalapril for at least two years previous to this incident (Landi et al, 2003).

### 3.3.3.F Metabolic finding

**1)** Summary

**a)** The manufacturer reports that INCREASED APPETITE (3-6%) and WEIGHT GAIN (5-6%) have occurred with olanzapine therapy. (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a).

**2)** Weight gain, increased appetite, increases in serum triglycerides, and hyperglycemia have been reported with olanzapine administration.

**3)** Olanzapine-induced KETOACIDOSIS has been reported, including one near fatal case in a 44-year-old African American woman. In the near fatal case, the patient had taken olanzapine 25 milligrams/day for approximately one month (Straker et al, 2002).

**4)** High dose olanzapine was associated with mild extrapyramidal symptoms (EPS), elevated serum prolactin and alanine aminotransferase (ALT) levels, and an average weight gain of 8 kilograms (kg) in 8 men with schizophrenia and schizoaffective disorder. These patients, who were resistant to typical neuroleptics and risperidone or clozapine at adequate doses, were dosed with olanzapine 20 to 40 milligrams (mg) for a mean of 40 weeks (Bronson & Lindenmayer, 2000).

**5)** A prospective, multicenter, observational study showed that olanzapine treatment of outpatients (n=2128) with schizophrenia was safer than in a control group of patients (n=821) receiving a variety of other antipsychotic drug therapies. Drugs used in the control group included risperidone, haloperidol, sertindole, zuclopenthixol, fluphenazine, thioridazine, perphenazine, pimozide, clozapine, pipotiazine, sulpiride, chlorpromazine, levomepromazine, clothiapine, and lorazepam. Overall, olanzapine had a significantly lower incidence of adverse events than the control group (48% versus 64%, p less than 0.001). Somnolence and weight gain occurred significantly more frequently in olanzapine-treated patients. Akathisia, dystonia, extrapyramidal syndrome, hypertonia, and tremor were significantly higher in the control group. Abnormal ejaculation and impotence occurred significantly more frequently in men in the control group. Over a 6-month period, fewer olanzapine-treated patients received a concomitant anticholinergic medication in comparison to patients in the control group (36% versus 58%, p less than 0.001) (Gomez et al, 2000).

**6)** LITERATURE REPORTS

**a)** Adolescent patients taking olanzapine experienced greater weight gain and increased in body mass index (BMI) than patients taking quetiapine in a retrospective study involving 103 patients younger than 18 years of age. Patients received olanzapine (n=50, mean daily dose 13.9 milligrams (mg)) or quetiapine (n=53, mean daily dose 510.9 mg) for at least 2 weeks. Weight and height were measured at baseline and 14 or more days after baseline. Average weight gain from baseline in the olanzapine group was 3.8 kilograms (kg) (p less than 0.001) compared to 0.03 kg in the quetiapine group. Both the olanzapine and quetiapine groups showed slight, but significant, increases in height from baseline (0.006 meters, p=0.042 and 0.006 meters, p less than 0.001, respectively). After controlling for baseline differences, the mean weight change between groups was significant (3.4 kg, p less than 0.001). BMI increased by an average of 1.3 kg per square meter (m(2)) in the olanzapine group (p less than 0.001) compared to a decreased of 0.2 kg/m(2) in the quetiapine group. After controlling for baseline differences, the mean difference in change in BMI was significant (0.9 kg/m(2), p=0.008) (Patel et al, 2004).

**b)** In a continuing day-treatment program 15 out of 16 patients receiving olanzapine gained weight. The mean weight gain was 22 pounds with a mean olanzapine dose of 14 milligrams (mg) and mean treatment duration of 7 months (Gupta et al, 1999).

**c)** Weight gain has been observed in recipients of olanzapine (mean of 3.5 kilograms (kg) with 12.5 to 17.5 milligrams (mg) daily) (Beasley et al, 1996) and is most pronounced in patients on initial doses of 15 mg or above (Prod Info Zyprexa(R), 1998).

**d)** EXCESSIVE APPETITE was seen more commonly with olanzapine therapy than with haloperidol (24% versus 12.4%,p less than 0.05). Olanzapine therapy was also associated with a clinically significant greater increase in weight over haloperidol therapy (p less than 0.001). However, a post hoc analysis revealed that body mass index was the predominant predictor of weight gain. Patients with a low prestudy body mass index were more likely to gain weight during olanzapine treatment. Treatment effect on weight change was consistent between male and female patients (Tollefson et al, 1997a).

### 3.3.3.G Prolactin level raised

**1)** Summary

**a)** A case a GALACTORRHEA with elevated serum prolactin levels was reported in a 33-year-old woman after receiving olanzapine (5 to 20 milligrams (mg)/day) for the treatment of schizophreniform disorder. During the fifth week of olanzapine therapy, the patient developed spontaneous whitish discharge from both breasts and reported missing her menstrual period. Her serum prolactin level was 146.55 nanograms/milliliter (ng/mL) (normal range, 1.5 to 19 ng/mL). Olanzapine was discontinued and replaced with quetiapine (25 to 100 mg/day). Symptoms of galactorrhea resolved within 3 weeks of stopping olanzapine, and serum prolactin levels began to decrease. Quetiapine therapy was continued without recurrence of galactorrhea (Mendhekar et al, 2004).

**b)** High dose olanzapine was associated with mild extrapyramidal symptoms (EPS), elevated serum prolactin and alanine aminotransferase (ALT) levels, and an average weight gain of 8 kilograms (kg) in

8 men with schizophrenia and schizoaffective disorder. These patients, who were resistant to typical neuroleptics and risperidone or clozapine at adequate doses, were dosed with olanzapine 20 to 40 milligrams (mg) for a mean of 40 weeks (Bronson & Lindenmayer, 2000).

**c)** Olanzapine has produced small elevations in serum prolactin [about 0.1 to 0.2 nanomoles/liter(nmol/L)], which have tended to be dose- related. However, significantly greater increases have occurred with haloperidol (Anon, 1994a); (Beasley et al, 1996). Cases of unwanted pregnancies have been reported after switching from conventional neuroleptic medications to olanzapine possibly due to a normalization of prolactin levels and a potential return of FERTILITY (Dickson & Dawson, 1998).

### 3.3.3.H Serum triglycerides raised

**1)** Summary

**a)** Increases in serum triglycerides have been reported with olanzapine therapy (Osser et al, 1999); (Sheitman et la, 1999).

**2)** LITERATURE REPORTS

**a)** Patients (n=25) receiving olanzapine were found to have increases in their weight and serum triglycerides (Osser et al, 1999). In an open study, patients receiving olanzapine [mean dose 13.8 milligrams(mg)] had their weight, cholesterol, and triglycerides measured at baseline and after 12 weeks. Weight increased by a mean of 5.4 kg. Cholesterol levels increased by only 3 milligrams/deciliter (mg/dL) while triglyceride levels increased by 60 mg/dL. The triglyceride change was highly associated with weight change (p less than 0.02).

**b)** After an average of 16 months of olanzapine therapy, 9 patients had marked increases in triglyceride levels (Sheitman et la, 1999). Triglyceride levels increased from a mean of 170 milligrams/deciliter (mg/dL) to a mean of 240 mg/dL. Five patients had at least a 50% increase in levels. Cholesterol levels remained essentially unchanged. The patients had a mean weight gain of 10 kilograms (kg).

## 3.3.4 Gastrointestinal Effects

### 3.3.4.A Constipation

**1)** Summary

**a)** The manufacturer reports that constipation (9-11%) has occurred with olanzapine therapy (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a). A relatively common adverse gastrointestinal effect of olanzapine is constipation (secondary to anticholinergic activity), which appears to be dose-related (Anon, 1995); (Beasley et al, 1996). In patients receiving a mean of 12 milligrams (mg) daily and 16 mg daily, respective incidences of constipation were 8% and 15% (Beasley et al, 1996). The incidence of constipation with olanzapine in higher doses (12.5 to 17.5 mg daily) is greater than observed with haloperidol 10 to 20 mg daily (Beasley et al, 1996). Anticholinergic effects, which include constipation, are common adverse effects of olanzapine therapy (Isbister et al, 2001); (Beasley et al, 1996)(Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a).

**2)** Incidence: 5-6%

### 3.3.4.B Excessive salivation

**1)** Summary

**a)** Hypersalivation has occurred with olanzapine therapy. A 20-year- old woman experienced morning grogginess and soaking her pillow with saliva during sleep while receiving olanzapine 10 milligrams/day (mg/d). Her symptoms worsened with an increased dose (Perkins & McClure, 1998). Increased salivation has been reported in premarketing clinical trials and in an accidental

pediatric ingestion (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a; Yip & Graham, 1997).

**3.3.4.C Gastrointestinal tract finding**

**1)** Summary

**a)** The manufacturer reports that INCREASED SALIVATION, THIRST and DYSPEPSIA (7-11%) have occurred with olanzapine therapy. ESOPHAGEAL DYSMOBILITY has been associated with antipsychotic therapy. (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a). Dyspepsia is not dose-related. (Beasley et al, 1996). ANTICHOLINERGIC EFFECTS, including DECREASED BOWEL SOUNDS, are common adverse effects of olanzapine therapy. These effects are dose-related (Isbister et al, 2001); (Beasley et al, 1996)(Prod Info Zyprexa(R), 1996). There has also been one case report of acute hemorrhagic pancreatitis (Doucette et al, 2000).

**2)** The manufacturer reports that constipation, increased salivation, vomiting, thirst, dry mouth, dyspepsia, and nausea have occurred with olanzapine therapy. Dry mouth and nausea appear to be dose-related. Esophageal dysmobility has been associated with antipsychotic therapy.

**3.3.4.D Nausea and vomiting**

**1)** Summary

**a)** Vomiting (4%) and nausea (greater than or equal to 2%) have occurred with olanzapine therapy. Nausea appears to be dose-related. The incidence of nausea tends to increase with dose (2% with 12 milligrams (mg) daily, 9% with 16 mg daily) and in higher doses (12.5 to 17.5 mg daily) is greater than observed with haloperidol 10 to 20 mg daily (Beasley et al, 1996)(Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a).

**3.3.4.E Pancreatitis**

**1)** Summary

**a)** ACUTE HEMORRHAGIC PANCREATITIS has been reported as a probable adverse event of olanzapine. Olanzapine was started 6 days prior to the onset of symptoms. Other concomitant drugs were ruled out as contributing to pancreatitis. Death due to secondary unrelenting peritonitis occurred in this case (Doucette et al, 2000). This is a rare adverse effect of olanzapine.

**b)** In one study of reported cases (n=192) of antipsychotic-induced pancreatitis, 33% of the cases were associated with the use of olanzapine at a mean daily dose of 15 milligrams. In most patients, time to onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003c).

**c)** Olanzapine was the probable cause of acute hemorrhagic pancreatitis in a 72-year-old female admitted with abdominal pain and an accidental verapamil overdose. Past medical history included multiple sclerosis, left temporal cerebral infarct (2 weeks prior to admission), depression, chronic pain, and drug abuse. Prior to admission she was taking ketorolac, morphine, and temazepam. Olanzapine (5 milligrams (mg) daily) had been initiated 6 days prior to admission for recent cognitive decline. The patient's chief complaint of abdominal pain began 24 hours before admission for which she inadvertently ingested 10 of her husband's verapamil 240 mg sustained release tablets. Laparotomy revealed hemorrhagic pancreatitis. Despite supportive care, the patient died due to peritonitis related to pancreatitis. Using the Naranjo Probability Scale, olanzapine was considered to be the probable cause of acute pancreatitis in this patient (Doucette, 2000). Other authors have pointed out possible discrepancies in the above case such as the use of multiple medications and chronic alcoholism which they believe could have contributed to the acute pancreatitis (Woodall & DiGregorio, 2001).

**3.3.4.F Xerostomia**

**1)** Summary

**a)** The manufacturer reports that dry mouth (9-22%) has occurred with olanzapine therapy. Dry mouth appears to be dose-related (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a). A relatively common adverse gastrointestinal effect of olanzapine is dry mouth (secondary to anticholinergic activity), which appears to be dose-related (Anon, 1995); (Beasley et al, 1996). In patients receiving a mean of 12 milligrams (mg) daily and 16 mg daily, respective incidences of dry mouth were 5% and 13% (Beasley et al, 1996). The incidence of dry mouth with olanzapine in higher doses (12.5 to 17.5 mg daily) is greater than observed with haloperidol 10 to 20 mg daily (Beasley et al, 1996). Anticholinergic effects, which include dry mouth, are common adverse effects of olanzapine therapy (Isbister et al, 2001); (Beasley et al, 1996)(Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a).

**2)** Incidence: 5-15%

### 3.3.5 Hematologic Effects

#### 3.3.5.A Agranulocytosis

**1)** Summary

**a)** Fifteen days after starting olanzapine (5 milligrams daily), a 46-year-old male presented to the hospital with fever, chills, and odinophagia. He was also concurrently taking cyanamide. A white blood cell count of 0.5 x 10(9)/liter (L) with a neutrophil count of 0.36 x 10(9)/L was noted. Olanzapine and cyanamide were stopped and antibiotic therapy was initiated. By the sixth hospital day, his white blood cell count had normalized. A temporal relationship between olanzapine therapy and new onset agranulocytosis was noted (Tolosa-Vilella et al, 2002).

**b)** Unlike clozapine, a structurally related drug, olanzapine has not been shown in preclinical trials to cause any significant agranulocytosis (Tollefson et al, 1997a); (Beasley et al, 1996)(Anon, 1994a; Anon, 1995). However, due to the structural similarities of the two drugs, there may be a potential for abnormal hematologic reactions. Subsequently, however, there have been reports of agranulocytosis with olanzapine administration (Oyewumi & Al-Semaan, 2000); (Fachinfo, Zyprexa(R), 1998)(Naumann et al, 1999). There have also been several cases of olanzapine adversely prolonging the recovery time of clozapine-induced granulocytopenia reported (Konakanchi et al, 2000).

**c)** Neutropenia was reported in a 39-year-old African American woman receiving olanzapine for paranoid schizophrenia. Prior to olanzapine, she had received clozapine for 7 years, but this was discontinued due to the development of granulocytopenia. Concurrent medications included divalproex sodium 1000 milligrams (mg) three times daily (TID), nifedipine 60 mg daily, metformin 1000 mg TID, insulin 70/30 (20 units in the morning, 10 units in the evening) and lorazepam 2 mg QD. Her absolute neutrophil count (ANC) was 3,110/millimeter (mm). The patient's absolute ANC was 1410 cells per millimeter (/mm) at the time clozapine was switched to olanzapine (10 mg QD). After 7 days of olanzapine, ANC increased to 1810 cells/mm, but by day 14, it had decreased to 1050 cells/mm. Olanzapine was reintroduced 6 months later without incident. It may be prudent to delay initiating olanzapine therapy in patients with clozapine-induced granulocytopenia until the patient's hematologic status has normalized (Konakanchi et al, 2000).

**2)** LITERATURE REPORTS

**a)** During clozapine-induced agranulocytosis in 2 patients with schizophrenia, olanzapine [doses greater than 25 milligrams/day (mg/d)] was shown to be a safe and effective treatment. Additionally, olanzapine did not worsen the severe neutropenia or agranulocytosis nor did it prevent recovery (Oyewumi & Al-Semaan, 2000).

**b)** A 27-year-old man who had been previously treated with clozapine therapy and had a normal leukocyte count, developed agranulocytosis with olanzapine. Five months after discontinuing clozapine therapy, olanzapine therapy was begun and rapidly increased to 40 milligrams (mg) daily. After 9 days his white blood cell (WBC) count decreased to 3.4 x 10(9)/Liter (L). Olanzapine therapy was discontinued and 2 days later his WBC count had decreased to 2.3 x 10(9)/L. His neutrophil count also decreased to 0.39 x 10(9)L. He was successfully treated with granulocyte colony-stimulating

factor 5 micrograms/kilogram (mcg/kg)(Naumann et al, 1999).

**c)** Thirty-two patients with a history of clozapine-induced neutropenia or agranulocytosis did not experience decreased neutrophil counts during olanzapine treatment (Prod Info Zyprexa(R), 1998). However, clinical experience with olanzapine, especially with long-term use, remains limited.

**3.3.5.B Hematology finding**

**1)** Significant hematologic abnormalities have not been reported during olanzapine therapy in available studies. However, agranulocytosis, leukopenia and neutropenia have been reported rarely with olanzapine administration.

**3.3.5.C Leukopenia**

**1)** Summary

**a)** Unlike clozapine, a structurally related drug, olanzapine has not been shown in preclinical trials to cause any significant leukopenia (Beasley et al, 1996)(Anon, 1994a; Anon, 1995). However, due to the similarities of the two drugs, there may be a potential for abnormal hematologic reactions. Several cases of olanzapine adversely prolonging the recovery time of clozapine-induced granulocytopenia have been reported (Konakanchi et al, 2000).

**2)** LITERATURE REPORTS

**a)** Two patients treated with olanzapine for levodopa-induced psychosis developed leukopenia. A 56-year-old woman experienced decreased leukocytes (2400 microliters) after 4 months of therapy. She was tapered off olanzapine and recovered over 4 weeks. She was then started on clozapine and had a similar reaction. In the other case, a 58-year-old man who had previously had a decline in his white blood cell count (WBC) due to clozapine therapy, had a decline in his WBC (2100 microliters) 13 months after starting olanzapine therapy. After discontinuation of olanzapine, his WBC count returned to normal after 2 weeks (Meissner et al, 1999).

**3.3.5.D Neutropenia**

**1)** Summary

**a)** Significant hematologic abnormalities have not been reported during olanzapine therapy in available studies (Tollefson et al, 1997a); (Beasley et al, 1996)(Anon, 1994a; Anon, 1995). However, neutropenia has been reported with olanzapine therapy (Oyewumi & Al-Semaan, 2000; Prod Info Zyprexa(R), 1998; Benedetti et al, 1999). Unlike clozapine, a structurally related drug, olanzapine has not been shown in preclinical trials to cause any significant leukopenia or agranulocytosis. However, due to the similarities of the two drugs, there may be a potential for abnormal hematologic reactions. Several cases of olanzapine adversely prolonging the recovery time of clozapine-induced granulocytopenia have been reported (Konakanchi et al, 2000).

**2)** LITERATURE REPORTS

**a)** A patient previously treated with clozapine developed neutropenia associated with olanzapine therapy. A 48-year-old African American male with schizoaffective disorder (bipolar type), chronic paranoid schizophrenia, and schizoid personality disorder, had been maintained on clozapine 550 milligrams (mg) daily (QD) for over 1 year. His white blood cell (WBC) count ranged from 4000 to 6000 cells per cubic millimeter (/mm(3)) during that time. Clozapine was discontinued, however, when the absolute neutrophil count (ANC) fell below 1000 cells/mm(3). After 11 days off clozapine, the WBC count increased to 7300 cells/mm(3) (ANC not reported). Olanzapine therapy was initiated at 10 mg QD and titrated to 30 mg QD over a 2-week period. After 1 week (olanzapine dose 15 mg at bedtime), WBC fell to 5500 cells/(mm(3) At 30 mg/day, the WBC count decreased to 4800 cells/mm(3) (ANC 974 cells/ mm(3)). Olanzapine was discontinued and the patient's WBC count slowly began to return to normal, and then remained stable. This case suggests that patients who have previously taken clozapine may have an increased risk for neutropenia with olanzapine (Teter et al,

2000).

**b)** A 60-year-old African American male with chronic undifferentiated schizophrenia had been treated with clozapine, but this was discontinued during gallbladder surgery. While receiving clozapine, his WBC counts ranged between 4000 and 6000 cells/mm(3). Two years later, he received a 10-month course of olanzapine (30 mg QD), which was discontinued due to hyperglycemia and weight gain. Olanzapine (20 mg/d) was later restarted, and over a 17-month period, the patient's WBC count declined to 3100 cells/mm(3) with an ANC of 1023 cells/mm(3). Olanzapine was again discontinued, and after 5 days, the patient's WBC count had risen to 4500 cells/mm(3) with an ANC of 1986 cells/ mm(3). Olanzapine was restarted at 10 mg/day, with hematologic monitoring performed every other day. Within 1 week, the patient's WBC count again declined to 4100 cells/mm(3) with an ANC of 1860 cells/ mm(3). Olanzapine was continued with intensive monitoring. The patient's WBC ranged between 4000 and 5000 cells/mm(3). This case suggests that patients who have previously taken clozapine may have an increased risk for neutropenia with olanzapine. Teter et al, 2000).

**c)** During clozapine-induced agranulocytosis in 2 patients with schizophrenia, olanzapine [doses greater than 25 milligrams/day (mg/d)] was shown to be a safe and effective treatment. Additionally, olanzapine did not worsen the severe neutropenia or agranulocytosis nor did it prevent recovery (Oyewumi & Al-Semaan, 2000).

**d)** A 31-year-old woman who had previously experienced neutropenia with clozapine, experienced neutropenia secondary to olanzapine (Benedetti et al, 1999). Olanzapine was introduced 5 days after clozapine withdrawal; the neutrophil count had normalized to 2.6 x 10(9)/liter (L). Olanzapine 5 milligrams (mg) was given on the first day and 10 mg daily starting on the second day. After 1 week, her neutrophil count decreased to 0.9 x 10(9)/L. Olanzapine was discontinued and the neutrophil count normalized after 4 weeks.

**e)** Thirty-two patients with a history of clozapine-induced neutropenia or agranulocytosis did not experience decreased neutrophil counts during olanzapine treatment (Prod Info Zyprexa(R), 1998). However, clinical experience with olanzapine, especially with long-term use, remains limited.

### 3.3.5.E Pancytopenia

**1)** Summary

**a)** Olanzapine was associated with pancytopenia and exacerbated motor disability in a patient with Parkinson's disease (Onofrj and Thomas, 2001).

**2)** LITERATURE REPORTS

**a)** Olanzapine was associated with pancytopenia and exacerbated motor disability in a 67-year-old man with Parkinson's disease. Olanzapine 5 milligrams (mg) daily (QD) was added to a regimen of levodopa 1.1 grams (g) and benserazide 275 mg QD to treat psychotic disturbances with hallucinations and paranoid delusions. After 1 week, the dose was increased to 10 mg/d. Complete blood count (CBC) values were within normal limits. After 2 weeks of therapy, visual hallucinations and delusions decreased in frequency, but motor symptoms, neck rigidity, upper and lower limb rigidity, and bradykinesia worsened. Levodopa was increased to 1.3 g/day and benserazide was increased to 325 mg/d. After 4 weeks of olanzapine treatment, the CBC showed a modest reduction in white blood cells (WBC), red blood cells (RBC), and platelets. One week later the hematological parameters continued to decline and olanzapine was discontinued. Subsequently, WBC, RBC, and platelet counts increased. Within 4 weeks of olanzapine withdrawal, counts were within normal limits and remained normal for the following year. This report suggests that olanzapine should be used with caution in patients with Parkinson's disease and that hematologic monitoring may be necessary (Onofrj and Thomas, 2001).

## 3.3.6 Hepatic Effects

### 3.3.6.A Increased liver function test

**1)** Summary

**a)** Increases in serum alanine aminotransferase (ALT) above 200 International Units/Liter (IU/L) occurred in 2% of patients (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a). Elevations of aspartate and alanine aminotransferases and gamma-glutamyl transferase (GGT) have been observed in approximately 10% of patients. These changes appear to be dose-dependent and are reversible upon withdrawal of therapy (Beasley et al, 1996). Close monitoring of liver function is advised, especially with use of higher doses and/or during prolonged olanzapine therapy (Bronson & Lindenmayer, 2000); (Beasley et al, 1996)(Prod Info Zyprexa(R), 1996).

**2)** LITERATURE REPORTS

**a)** Increases in serum alanine aminotransferase (ALT) above 200 International Units/Liter (IU/L) occurred in 2% of patients. In clinical trials, discontinuation due to transaminase increases occurred in about 1% (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a).

**b)** High dose olanzapine was associated with mild extrapyramidal symptoms (EPS), elevated serum prolactin and alanine aminotransferase (ALT) levels, and an average weight gain of 8 kilograms (kg) in 8 men with schizophrenia and schizoaffective disorder. These patients, who were resistant to typical neuroleptics and risperidone or clozapine at adequate doses, were dosed with olanzapine 20 to 40 milligrams (mg) for a mean of 40 weeks. Three patients experienced increases in serum ALT concentrations; in one patient also taking pravastatin, ALT rose from 28 to 113 units per liter (Bronson, & Lindenmayer, 2000).

**c)** In another trial, the incidence of TRANSAMINASEMIA was comparable to that seen with haloperidol (Tollefson et al, 1997a).

**d)** Elevations of aspartate and alanine aminotransferases and gamma-glutamyl transferase (GGT) have been observed in approximately 10% of patients (Beasley et al, 1996). These changes appear to be dose-dependent and are reversible upon withdrawal of therapy; clinical signs of hepatic dysfunction have not been reported in available trials. However, close monitoring of liver function is advised, especially with use of higher doses and/or during prolonged therapy.

**e)** The incidence of aminotransferase elevations was greater with olanzapine than with haloperidol in one trial (Beasley et al,1996).

### 3.3.6.B Liver finding

**1)** Elevated liver function tests are reported with olanzapine therapy.

## 3.3.7 Immunologic Effects

### 3.3.7.A Immunology finding

**1)** Summary

**a)** FLU SYNDROME (greater than 1%) has occurred with olanzapine therapy (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a). Olanzapine-induced HYPERSENSITIVITY syndrome, consisting of fever, rash, eosinophilia and toxic hepatitis, has been reported in a 34-year-old man 60 days after initiation of olanzapine therapy. Symptoms resolved following the discontinuation of olanzapine. Skin and liver biopsies confirmed drug-induced hypersensitivity syndrome (Raz et al, 2001).

**2)** Hypersensitivity syndrome and flu syndrome have occurred with olanzapine therapy.

## 3.3.8 Musculoskeletal Effects

### 3.3.8.A Musculoskeletal finding

**1)** Summary

**a)** The manufacturer reports that BACK PAIN, JOINT PAIN (5%), EXTREMITY PAIN (5%), and

TWITCHING (greater than 1%) have been associated with olanzapine therapy (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a). Asymptomatic ELEVATED CREATINE PHOSPHOKINASE (CPK) have been reported during clinical trials (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a). Marked elevation of serum creatine kinase (CK) associated with olanzapine therapy, with no other diagnostic criteria for neuroleptic malignant syndrome, has been reported. No psychomotor agitation was present. Drug discontinuation resulted in return to baseline of serum CK (Marcus et al, 1999).

**2)** Back pain, joint pain, extremity pain, elevated creatine phosphokinase and twitching are reported with olanzapine therapy.

### 3.3.9 Neurologic Effects

#### 3.3.9.A Cerebrovascular disease

**1)** Summary

**a)** The manufacturer has reported an annual incidence of 41.6 cerebrovascular adverse events (ie, STROKE, TRANSIENT ISCHEMIC ATTACK) per 1000 patient years in olanzapine-treated elderly patients with **dementia**. A pooled analysis of five double-blind, placebo-controlled trials revealed a significantly higher incidence of cerebrovascular adverse events in elderly patients with **dementia**-related psychosis who were treated with olanzapine as compared with placebo (1.3% vs 0.4%, respectively) (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a; Pers Comm, 2004).

#### 3.3.9.B Disturbance in speech

**1)** Summary

**a)** Four older patients (70 to 86 years old) presented with SPEECH DYSFUNCTION or general decreases in function after receiving olanzapine 5 to 10 milligrams/day (mg/d). Within 3 days to 4 weeks patients developed the inability to articulate clearly or unintelligible SLURRED SPEECH. Also noted was a decline in their level of functioning in the presence of increased or new incontinence, inability to feed oneself, and unsteady gait. Patients returned to their previous level of functioning once the olanzapine was discontinued (Gail & Noviasky, 1998).

#### 3.3.9.C Extrapyramidal disease

**1)** Summary

**a)** The manufacturer reports that extrapyramidal events occurred in 15% to 32% of patients, specific occurrences were: PARKINSONISM 8% to 20%, AKATHISIA 5% to 11%, DYSTONIC EVENTS 2% to 3%, DYSKINESIA, TARDIVE DYSKINESIA, and other residual events (MOVEMENT DISORDER, MYOCLONUS, TWITCHING) 1% to 5% (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a). Extrapyramidal symptoms have not been significant during olanzapine therapy of schizophrenia (Glazer, 2000a; Tollefson et al, 1997a); (Beasley et al, 1996)(Anon, 1994a; Beasley et al, 1996a). HYPERTONIA and akathisia have been reported in less than 9% of patients treated, with parkinsonian TREMOR occurring in approximately 5%; these effects have tended to be dose-related (Tollefson et al, 1997a; Anon, 1995); (Beasley et al, 1996)(Anon, 1994a).

**b)** A prospective, multicenter, observational study showed that olanzapine treatment of outpatients (n=2128) with schizophrenia was safer than in a control group of patients (n=821) receiving a variety of other antipsychotic drug therapies. Drugs used in the control group included risperidone, haloperidol, sertindole, zuclopenthixol, fluphenazine, thioridazine, perphenazine, pimozide, clozapine, pipotiazine, sulpiride, chlorpromazine, levomepromazine, clothiapine, and lorazepam. Overall, olanzapine had a significantly lower incidence of adverse events than the control group (48% versus

64%, p less than 0.001). Somnolence and weight gain occurred significantly more frequently in olanzapine-treated patients. Akathisia, dystonia, extrapyramidal syndrome, hypertonia, and tremor were significantly higher in the control group. Abnormal ejaculation and impotence occurred significantly more frequently in men in the control group. Over a 6-month period, fewer olanzapine-treated patients received a concomitant anticholinergic medication in comparison to patients in the control group (36% versus 58%, p less than 0.001) (Gomez et al, 2000).

**2)** LITERATURE REPORTS

**a)** High dose olanzapine was associated with mild extrapyramidal symptoms (EPS), elevated serum prolactin and alanine aminotransferase (ALT) levels, and an average weight gain of 8 kilograms (kg) in 8 men with schizophrenia and schizoaffective disorder. These patients, who were resistant to typical neuroleptics and risperidone or clozapine at adequate doses, were dosed with olanzapine 20 to 40 milligrams (mg) for a mean of 40 weeks. Several patients experienced rigidity alone or combined with cogwheeling of the elbow, wrist, or shoulder joints. (Bronson and Lindenmayer, 2000).

**b)** The incidence of extrapyramidal symptoms (EPS) as a result of antipsychotic treatment was less in olanzapine-treated patients than in risperidone-treated patients. This finding was confirmed in an international, multicenter, double-blind, prospective study involving 339 patients. The patients were treated with mean doses of olanzapine 17 milligrams/day (mg/d) or risperidone 7 milligrams/day (mg/d) for 28 weeks. The use of risperidone was also associated with greater use of anticholinergic medications. Data suggests that the therapeutic dose threshold for EPS may be wider for olanzapine than for risperidone, but more studies are needed for verification (Glazer, 2000a).

**c)** Extrapyramidal effects have occurred in clinical trials and appear to be dose-related (greater than 20 mg/day) (Bronson & Lindenmayer, 2000). Hypertonia and akathisia have been reported in less than 9% of treated patients, with parkinsonian tremor occurring in approximately 5% (Anon, 1995); (Beasley et al, 1996)(Anon, 1994a; Prod Info Zyprexa(R), 1996). The elderly appear to be more sensitive to extrapyramidal side effects of olanzapine (Granger & Hanger, 1999).

**d)** An 81-year-old woman treated with olanzapine 5 mg daily developed RIGIDITY and HYPERTONICITY. She had no history of parkinsonism and creatine kinase levels were normal. She had been independent but over several weeks declined, eventually requiring the assistance of 2 nurses for transfers. Olanzapine was stopped and within 1 week, she was totally independent again (Granger & Hanger, 1999).

**e)** A rate of 1.4% has been reported for acute dystonic reactions in patients taking olanzapine. Two case reports include a 50- year-old man and a 68-year-old woman who had severe TORTICOLLIS and LINGUAL DYSTONIA with dysarthria, respectively. Both were controlled with anticholinergic agents (Landry & Cournoyer, 1998).

**f)** In comparative studies lasting up to 1 year, olanzapine treatment has been associated with a significantly reduced incidence of dyskinesias. The risk of delayed dyskinesias, however, increases with prolonged treatment. Dose reductions or treatment discontinuation must be considered at the first sign of such reactions (Fachinfo Zyprex(R), 1998).

**g)** In one comparative trial, akathisia, tremor, and dystonia were reported in 16%, 15%, and 13% of schizophrenic patients, respectively, receiving haloperidol [mean, 16 milligrams (mg) daily]. Corresponding incidences in those treated with olanzapine in higher doses (mean, 16 mg daily) were 7%, 6%, and 0%. In studies, olanzapine has produced numeric improvements relative to baseline in the Simpson-Angus scale (for parkinsonian tremor) and Barnes scale (for akathisia) during treatment, whereas numerical worsening of these scales occurred in haloperidol-treated patients (Tollefson et al, 1997a); (Beasley et al, 1996).

### 3.3.9.D Neuroleptic malignant syndrome

**1)** Summary

**a)** Neuroleptic malignant syndrome (NMS), due to dopaminergic blockade, associated with olanzapine therapy has been reported, but is rare. Patients taking concomitant or recently discontinued neuroleptics appear to be more susceptible to drug-induced NMS. CPK serum levels are usually elevated; urine myoglobin levels may be elevated; and high fever and rigidity are present. Generally

after stopping the drug therapy and administering supportive therapies, NMS resolves (Stanfield & Privette, 2000; Nyfort-Hansen & Alderman, 2000; Sierra-Biddle et al, 2000; Margolese, 1999; Levenson, 1999; Gheorghiu et al, 1999); (Burkhard et al, 1999)(Apple & Van Hauer, 1999; Cohen et al, 1999); (Johnson & Brusner, 1998)(Moltz & Coeytaux, 1998; Filice et al, 1998).

**b)** Symptoms have begun as early as 2 to 4 days and as late as 1 year. Patients have presented with typical symptoms of NMS including HYPERTHERMIA, MUSCLE RIGIDITY, MENTAL STATUS CHANGES, and AUTONOMIC INSTABILITY. Increases in serum creatine kinase have ranged from 762 International Units/Liter (IU/L) to 41,900 IU/L. Some patients previously had NMS with other neuroleptics including risperidone and haloperidol. All patients recovered after discontinuation of olanzapine and with treatments including dantrolene, bromocriptine, or benzodiazepines. One other possible case was reported, however, the patient was also receiving clozapine and no rigidity was noted (Moltz & Coeytaux, 1998).

**2)** LITERATURE REPORTS

**a)** ATYPICAL NEUROLEPTIC MALIGNANT SYNDROME, also described as fever- delirium-autonomic instability syndrome, has been reported in at least one patient. A 30-year-old man developed fever, difficulty swallowing, sinus tachycardia, delirium, elevated white blood count, and elevated creatine kinase two days after olanzapine (10 milligrams/day) was initiated for the treatment of violent behavior. No rigidity, hyperreflexia, hyporeflexia, or muscle weakness was observed. Olanzapine was discontinued and symptoms completely resolved within 2 days (Robinson et al, 2003).

**b)** A 23-year-old woman developed clinical features consistent with neuroleptic malignant syndrome (NMS) while receiving olanzapine 5 milligrams (mg) daily (QD) for schizoaffective disorder. Other medications included lithium and fluoxetine. After 40 days of olanzapine therapy, the patient lapsed into a coma. On admission to the hospital, her trunk and limbs were hypertonic and hyperextended, with generalized tremor. Symptoms included tachycardia, diaphoresis, blood pressure fluctuations, and an elevated body temperature of 38.6 degrees Celsius. Laboratory data showed 11,200 leukocytes with a left shift, metabolic acidosis, hypernatremia, hypokalemia, a lithium levels of 0.7 milliequivalents per liter (mEq/L), and a creatinine kinase (CK) level of 6,686. Cultures of cerebrospinal fluid and blood were negative. A urine toxicology screen was consistent with antidepressant use. Following supportive in an intensive care unit, the patient recovered fully (Sierra-Biddle et al, 2000).

**c)** A 42-year old man with a history of schizophrenia developed symptoms consistent with neuroleptic malignant syndrome 21 days after initiation of olanzapine therapy. At the onset of symptoms, the patient was also taking ranitidine, benztropine mesylate and cephalexin. Symptoms included severe respiratory distress, intermittent apnea, decreased mental status, fever (rectal temperature of 41 degrees Celsius), right- sided posturing to physical stimulus, rigid muscle tone, and dry mucous membranes. On admission, vital signs included a pulse of 164 beat per minute (min) and a blood pressure 111/79. Respiratory effort was absent. Laboratory tests revealed a serum creatinine phosphokinase (CPK) of 250 units/liter (u/L), white blood count 13,100, hemoglobin 12.4 grams %, hematocrit 35%, serum sodium 141 millimoles/liter (mmol/L), blood urea nitrogen 9 milligram (mg)/deciliter (dL), and serum creatinine 0.8 mg/dL. Olanzapine was discontinued. The patient was intubated and mechanically ventilated, treated with dantrolene, cooling blankets, bromocriptine and empiric antibiotic therapy. The patient's hospital course was complicated by pneumonia and prolonged ventilator dependence. At discharge, he demonstrated obvious cognitive deficits and left hemiplegia (Stanfield & Privette, 2000).

**d)** Other cases have reported only elevations in serum creatine kinase without other symptoms of NMS (Marcus et al, 1999).

### 3.3.9.E Neurological finding

**1)** Summary

**a)** The manufacturer reports that the following adverse reactions have occurred with olanzapine therapy: SOMNOLENCE (20-35%), INSOMNIA (12%), DIZZINESS (11-18%), AKATHISIA (3-5%), HYPERTONIA (3%), TREMOR (4-7%), and ARTICULATION IMPAIRMENT (2%). Somnolence and tremor appear to be dose-related. (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R),

Zyprexa(R) IntraMuscular Olanzapine, 2004a). Olanzapine has been shown to have acute central nervous system depressant effects in humans during clinical trials. Dose-related somnolence is the most frequent adverse effect, occurring at an incidence of 26%, and appears to be dose-related. ASTHENIA and dizziness have occurred in 10% and 8% to 15% of patients, respectively, in clinical trials (Beasley et al, 1996).

**2)** Somnolence, insomnia, nervousness, dizziness, akathisia, hypertonia, tremor, parkinsonism, tardive dyskinesia and articulation impairment are reported with olanzapine administration.

**3.3.9.F Parkinsonism**

**1)** Summary

**a)** Contrary to common belief, the results of a retrospective cohort study suggest that atypical antipsychotics may not be safer than typical antipsychotics when dose and potency are considered (Rochon et al, 2005).

**b)** In a retrospective review of 12 Parkinson's disease patients receiving olanzapine, only 1 patient was able to continue the medication without worsening of disease (Molho & Factor, 1999). Several other studies also reported a worsening of PARKINSON'S DISEASE symptoms with olanzapine therapy (Granger & Hanger, 1999; Rudolf et al, 1999; Jimenez-Jimenez et al, 1998).

**2)** LITERATURE REPORTS

**a)** The results of a cohort study indicate that high-dose atypical antipsychotic therapy carries a similar risk for the development of parkinsonism as does typical antipsychotic therapy. In a population-based, retrospective cohort study, adults (aged 66 years and older) with evidence of **dementia** were followed for up to 1 year for the development of parkinsonism symptoms associated with typical or atypical antipsychotic use. As compared with older adults receiving atypical antipsychotic therapy (ie, olanzapine, risperidone, quetiapine), incident parkinsonism was 30% more likely to occur in those taking typical antipsychotics (ie, chlorpromazine, haloperidol, perphenazine) (adjusted HR, 1.3; 95% CI, 1.04 to 1.58), and 60% less likely to occur in patient who did not receive either therapy (HR, 0.4; 95% CI, 0.29 to 0.43). Older adults using higher potency typical antipsychotics had almost a 50% greater risk of experiencing parkinsonism as compared with patients prescribed atypical antipsychotics (all were considered lower potency) (HR, 1.44; 95% CI, 1.13 to 1.84); however, in patients receiving lower potency typical antipsychotics, the risk of developing parkinsonism was no different from that in adults taking atypical antipsychotics (HR, 0.75; 95% CI. 0.48 to 1.15). In addition, a positive dose-related relationship was observed between the occurrence of incident parkinsonism and the use of atypical antipsychotics. The risk for developing parkinsonism was more than twice as great in patients using a high-dose atypical antipsychotic agent as compared with those prescribed a low-dose atypical antipsychotic agent (HR, 2.07; 95% CI, 1.42 to 3.02). Furthermore, patients taking a typical antipsychotic were found to have a similar risk for the development of parkinsonism as patients receiving high-dose atypical antipsychotic therapy (p=ns). The authors conclude that atypical antipsychotics may not be safer than typical antipsychotics when dose and potency are considered (Rochon et al, 2005).

**b)** In a retrospective review of 12 Parkinson's disease patients receiving olanzapine, only 1 patient was able to continue the medication without worsening of disease. Nine out of 12 patients had their psychosis improve with olanzapine therapy. Nine out of 12 also had their motor function decline. In 6 patients with available Unified Parkinson's Disease Rating Scale scores, average declines in scores were 9 points. Only 1 patient remained on olanzapine therapy (Molho & Factor, 1999).

**c)** A 72-year-old man had his Parkinson's disease worsen with olanzapine treatment for hallucinations. The day after beginning olanzapine 5 milligrams (mg) he became very rigid. He was unable to stand or walk. After discontinuing olanzapine, his functioning returned over several days (Granger & Hanger, 1999).

**d)** A 68-year-old man with Parkinson's disease developed a severe akinetic-rigid syndrome after receiving olanzapine 10 milligrams (mg) for hallucinations. He was later successfully treated with clozapine (Rudolf et al, 1999).

**e)** Parkinson's disease was reported to worsen in 2 patients after olanzapine was substituted for

clozapine. Olanzapine-substitution was initiated to avoid hematological assessments. However, after 4 to 7 days, olanzapine 5 milligrams/day (mg/d) resulted in worsening AKINESIA, RIGIDITY, and psychiatric symptoms (Jimenez-Jimenez et al, 1998).

### 3.3.9.G Restless legs syndrome

**1)** Summary

**a)** CASE REPORT - A 41-year-old man developed restless legs syndrome while receiving olanzapine therapy for schizophrenia. Olanzapine 10 milligrams (mg) daily was initiated and increased to 20 mg daily after 6 weeks. At that time, he began to experience PARESTHESIAS of both legs occurring exclusively at rest and worsening at night. He experienced some relief by applying cold packs and walking around. A sleep lab evaluation also showed evidence of periodic leg movements in sleep. The dose was decreased to 10 mg daily with only a slight decrease in symptoms. Nine days later the patient discontinued olanzapine and the symptoms vanished immediately (Kraus et al, 1999).

### 3.3.9.H Seizure

**1)** Summary

**a)** Seizures have been reported in only 0.9% of patients in pre- marketing clinical trials of olanzapine. Patients with histories of seizures or conditions that lower the seizure threshold may be more prone to seizures following olanzapine therapy (Lee et al, 1999; Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a). Fatal status epilepticus has also been reported with olanzapine administration (Wyderski et al, 1999).

**2)** LITERATURE REPORTS

**a)** Drug interactions with other drugs that lower the seizure threshold, such as clomipramine, have been reported to result in seizures with concomitant olanzapine (Deshauer et al, 2000).

**b)** Fatal STATUS EPILEPTICUS associated with olanzapine therapy in a woman with no underlying cause or predisposing factors for seizure has been reported. She had been on olanzapine therapy for 5 months prior to the seizures. Subsequent to the seizures she died from secondary rhabdomyolysis and disseminated intravascular coagulation. The authors classified this as a probable adverse event due to olanzapine (Wyderski et al, 1999).

**c)** A 31-year-old woman with schizoaffective disorder, organic mental disorder due to anoxic brain injury, and generalized seizure disorder experienced 3 generalized TONIC-CLONIC SEIZURES 13 days after starting olanzapine. Previously, she had been seizure-free for 2 years. She had been abruptly switched from haloperidol 40 milligrams (mg) twice daily to olanzapine 5 mg twice daily. Her other medications included lithium, divalproex sodium, benztropine, bethanechol, nitrofurantoin, and docusate. Multiple confounding factors may have contributed to her seizures (Lee et al, 1999).

### 3.3.9.I Tardive dyskinesia

**1)** Summary

**a)** Tardive dyskinesia may occur occasionally with olanzapine (Glazer, 2000a; Ananth & Kenan, 1999; Herran & Vazquez-Barquero, 1999); (Tollefson, 1997a). Tardive dyskinesia has been reported during clinical trials (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a).

**2)** Incidence: rare

**3)** LITERATURE REPORTS

**a)** A 40-year-old woman developed tardive dystonia with olanzapine therapy for her psychosis. She had previously developed tardive dyskinesia with loxapine therapy. After beginning olanzapine 10 mg at bedtime, she developed severe, frequent TORTICOLLIS. She also displayed dysphonia, blepharospasm, and grimacing. She was switched to clozapine and her dystonia decreased by 50% after 4 months (Dunayevich & Strakowski, 1999).

**b)** Two cases of tardive dyskinesia associated with olanzapine therapy were described. A 30-year-old woman developed involuntary perioral movements 2 months after beginning olanzapine 10 milligrams/day (mg/d). She had previously experienced parkinsonism with her haloperidol therapy. A 65-year-old woman developed athetoid movements of the tongue and chewing movements of the jaw after 7 months of olanzapine 20 mg/d. She was switched to clozapine but the tardive dyskinesia continued (Herran & Vazquez-Barquero, 1999).
**c)** Tardive dyskinesia may occur occasionally with olanzapine. A patient diagnosed with paranoid schizophrenia was started on olanzapine 20 milligrams (mg) daily. Five years later, the patient developed abnormal movements of his upper extremities and neck. A diagnosis of olanzapine-induced tardive dyskinesia and dystonia was made after ruling out all other causes. The patient continued to receive olanzapine with improvement in his psychopathology but no improvement in his tardive dyskinesia (Ananth & Kenan, 1999).
**d)** A long-term follow-up study, which utilized results from 3 other studies, reported that haloperidol-treated patients (n=114) had a tardive dyskinesia (TD) incidence rate/year 12 times higher than that of olanzapine-treated patients (n=513). Both medications were in doses of 5 to 20 milligrams/day (mg/d) (Glazer, 2000a). (Tollefson, 1997a)
**e)** Data combined from 3 studies evaluating patients treated with olanzapine (n=707) or haloperidol (n=197) showed that olanzapine was associated with a lower incidence of tardive dyskinesia. At any visit after baseline, 7.1% of patients in the olanzapine group and 16.2% of patients in the haloperidol group manifested treatment-emergent tardive dyskinesia (p less than 0.001). At the last study visit, 2.3% of olanzapine patients and 7.6% of haloperidol patients manifested tardive dyskinesia (p equal to 0.001) (Tollefson, 1997a).

### 3.3.10 Ophthalmic Effects

#### 3.3.10.A Esotropia

**1)** Summary
**a)** Estropia was reported in a 14-year-old female who was taking Olanzapine and fluoxetine (Singh et al, 2000).
**2)** LITERATURE REPORTS
**a)** Esotropia developed in a 14-year-old African American female with psychotic depression, who received olanzapine 5 milligrams per day (mg/d) and fluoxetine 40 mg/d) for 6 months. The patient, who had no history of strabismus, complained of a severe headache, menorrhagia, eye irritation, and a "lazy eye." A neurologic examination revealed no focal neurologic findings. Computed tomography and magnetic resonance imaging of the head were normal. Within 1 week of discontinuation of olanzapine, diplopia and headache had cleared, with reported resolution of esotropia (Singh et al, 2000).

#### 3.3.10.B Eye / vision finding

**1)** Summary
**a)** The manufacturer reports that AMBLYOPIA (3%) and CONJUNCTIVITIS (greater than 1%) have been associated with olanzapine therapy (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a). Esotropia with diplopia and headaches have also been reported following olanzapine and fluoxetine therapy. When olanzapine was discontinued, symptoms cleared within one week (Singh et al, 2000).
**2)** Amblyopia, diplopia, esotropia and conjunctivitis are reported with olanzapine therapy.

### 3.3.12 Psychiatric Effects

#### 3.3.12.A Aggressive behavior

**1)** Summary

**a)** Two cases of patients developing AGITATION, CONFUSION, PARANOID BEHAVIOR and aggression have been reported (Jeshi, 1998). Two similar cases of aggression in patients beginning olanzapine were reported. The aggressive behavior worsened as the dose was increased (John et al, 1998). Agitation has been reported in up to 23% of olanzapine treated patients in clinical trials, as compared to 17% taking placebo. Agitation, insomnia, and nervousness may be a part of the disease process as opposed to a pharmacologic effect of the drug (Prod Info Zyprexa(R), 1996).

### 3.3.12.B Mania

**1)** Summary

**a)** Mania and hypomania have been described following olanzapine Administration (Aubrey et al, 2000)(Simon et al, 1999; Lindenmayer & Klebanov, 1998).

**2)** LITERATURE REPORTS

**a)** A review of the literature identified 10 cases of mania or hypomania related to olanzapine therapy. Patients were treated with 5 to 20 milligrams daily for schizophrenia (n=6), schizoaffective disorder (n=2), pervasive developmental disorder (n=1), or an unspecific psychotic disorder (n=1). The onset of development of manic symptoms ranged between 2 days and 35 days. Six of 10 patients were receiving no other medications; however, in the remaining 4 patients, the use of concomitant medications makes causality difficult to assess. Remission of symptoms occurred within 2 to 7 days after discontinuing olanzapine (n=6). In the other 4 patients, hypomania or mania resolved with a decrease in olanzapine dosage (Aubrey et al, 2000).

**b)** A 31-year-old woman with psychotic disorder experienced hypomania after receiving olanzapine 20 milligrams (mg) daily (Simon et al, 1999). On the second day of olanzapine therapy, she developed pressured speech, social disinhibition, and euphoric mood. Olanzapine was replaced by risperidone and her symptomatology remitted.

**c)** Two schizophrenic patients experienced manic-like activation after the start of olanzapine treatment. Both patients had failed other neuroleptic agents but had never experienced mania. In one case the mania resolved with a decrease in olanzapine dose from 20 milligrams (mg) to 10 mg daily. In the second case olanzapine was discontinued (Lindenmayer & Klebanov, 1998).

### 3.3.12.C Obsessive-compulsive disorder

**1)** Summary

**a)** Two cases of patients experiencing olanzapine-induced OBSESSIVE-COMPULSIVE DISORDER (OCD) were reported (Mottard & De La Sablonniere, 1999). A 35-year-old woman developed obsessive-compulsive disorder (OCD) after having olanzapine added to her fluvoxamine (Al-Mulhim et al, 1998). A 35-year-old man with schizophrenia and obsessive- compulsive disorder (OCD), had his OCD symptoms worsen after switching to olanzapine (Morrison et al, 1998).

**2)** LITERATURE REPORTS

**a)** Two cases of patients experiencing olanzapine-induced obsessive-compulsive disorder (OCD) were reported. Both patients had schizophrenia and were switched to olanzapine 15 to 25 milligrams (mg). The first man developed OCD 14 days after beginning olanzapine with symptoms of repeating words in his head and the compulsion to check doors. This disappeared with fluoxetine therapy. The second developed OCD symptoms after 3 months which included isolation, repeated hand-washing, checking doors and the alarm system. He also had impulsion phobias. He was successfully treated with clomipramine (Mottard & De La Sablonniere, 1999).

**b)** A 35-year-old woman developed obsessive-compulsive disorder (OCD) after having olanzapine 10 mg added to her fluvoxamine. She had a history of major depression with psychotic features, borderline personality, and bulimia. After 1 week she developed compulsive handwashing. Her fluvoxamine was changed to venlafaxine which successfully treated her OCD (Al-Mulhim et al, 1998).

**c)** A 35-year-old man with schizophrenia and obsessive-compulsive disorder (OCD), had his OCD symptoms worsen after switching to olanzapine (Morrison et al, 1998). His fluvoxamine was increased from 200 to 300 milligrams/day (mg/d) which helped control the OCD.

**3.3.12.D Panic attack**

**1)** Summary

**a)** CASE REPORT - A 36-year-old woman with schizophrenia began experiencing panic attacks after being switched from thioridazine to olanzapine. Olanzapine was started at 5 milligrams (mg) twice daily and increased to 3 times daily after 18 days. Panic attacks began after 24 days of treatment. They were successfully treated with alprazolam 0.5 mg as needed (Mandalos & Szarek, 1999).

**3.3.12.E Psychiatric sign or symptom**

**1)** Summary

**a)** The manufacturer reports that the following adverse reactions have occurred with olanzapine therapy: CONFUSION, and PERSONALITY DISORDER (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a). Relapse of psychiatric disease has also been seen with olanzapine administration (Kostakoglu et al, 1999). The manufacturer reports that INTENTIONAL INJURY and SUICIDE ATTEMPT have occurred with olanzapine therapy. (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a). KORO has been reported with olanzapine administration (Ramos & Budman, 1998).

**2)** Hostility, anxiety, aggression, koro and personality disorder are reported with olanzapine administration.

**3)** LITERATURE REPORTS

**a)** Two cases are reported where patients initially responded to olanzapine therapy and then relapsed after 6 weeks. Both received olanzapine titrated up to 20 milligrams (mg) over 2 to 3 weeks for chronic paranoid schizophrenia. A 38-year-old man showed a substantial improvement at the beginning of the fourth week through the sixth week. After 7 weeks, he had reemergence of the paranoid hallucinations, hostility, tension, and lack of judgment. A 35-year-old woman also had an increase in paranoid delusions and reemergence of auditory hallucinations, lack of judgment, insight, and poor impulse control at 8 weeks. The authors conclude that a rapid displacement of these drugs due to loose binding could play a role in early relapse (Kostakoglu et al, 1999).

**b)** A 19-year-old schizophrenic man developed KORO after having his olanzapine abruptly stopped to begin electroconvulsive therapy. He experienced a sudden overwhelming fear that his penis and left testicle were shrinking and receding into his abdomen despite his physical condition being normal. After 5 days, the olanzapine was restarted with his symptoms resolving (Ramos & Budman, 1998). Hostility and personality disorders associated with olanzapine have been reported in approximately 15% and 10% of patients treated, respectively, although the frequency of hostility was similar in placebo-treated patients (Beasley et al, 1996).

**3.3.13 Renal Effects**

**3.3.13.A Urinary incontinence**

**1)** Summary

**a)** There has been one reported case of urinary incontinence successfully treated with ephedrine following olanzapine use (Vernon et al, 2000).

**2)** LITERATURE REPORTS

**a)** Ephedrine successfully counteracted urinary incontinence associated with olanzapine in a 61-year-old man with bipolar disorder and alcohol abuse. The patient developed urinary incontinence when olanzapine (dose not reported) was added to lithium (dose not reported) for psychotic symptoms of

acute mania, psychosis, agitation, and verbalized homicidal thoughts. Incontinence remitted 24 hours after ephedrine (25 milligrams/day) was added to his regimen. (Vernon, 2000).

**3.3.13.B Urogenital finding**

**1)** Summary

**a)** The manufacturer reports that AMENORRHEA (1%), HEMATURIA (1%), METRORRHAGIA (1%), URINARY INCONTINENCE (2%), URINARY TRACT INFECTION (2%), and VAGINITIS (greater than 1%) have been associated with olanzapine therapy (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a).

**b)** A prospective, multicenter, observational study showed that olanzapine treatment of outpatients (n=2128) with schizophrenia was safer than in a control group of patients (n=821) receiving a variety of other antipsychotic drug therapies. Drugs used in the control group included risperidone, haloperidol, sertindole, zuclopenthixol, fluphenazine, thioridazine, perphenazine, pimozide, clozapine, pipotiazine, sulpiride, chlorpromazine, levomepromazine, clothiapine, and lorazepam. Overall, olanzapine had a significantly lower incidence of adverse events than the control group (48% versus 64%, p less than 0.001). Somnolence and weight gain occurred significantly more frequently in olanzapine-treated patients. Akathisia, dystonia, extrapyramidal syndrome, hypertonia, and tremor were significantly higher in the control group. Abnormal ejaculation and impotence occurred significantly more frequently in men in the control group. Over a 6-month period, fewer olanzapine-treated patients received a concomitant anticholinergic medication in comparison to patients in the control group (36% versus 58%, p less than 0.001) (Gomez et al, 2000).

**2)** Amenorrhea, hematuria, metrorrhagia, urinary incontinence, urinary tract infection, vaginitis and priapism are reported with olanzapine therapy.

**3.3.14 Reproductive Effects**

**3.3.14.A Priapism**

**1)** Summary

**a)** Priapism and instances of PAINFUL ERECTIONS have been reported with Olanzapine (Kuperman et al, 2001; Gordon & De Groot, 1999; Deirmenjian et al, 1998; Heckers et al, 1998).

**2)** LITERATURE REPORTS

**a)** Priapism developed in a 26-year old man treated with olanzapine 10 milligrams per day for disorganized schizophrenia. Although the patient was sexually overactive, he had previously taken varied psychotropic medications (including risperidone) without experiencing sexual side effects. Within 24 hours of discontinuation of olanzapine, priapism disappeared (Kuperman, 2000).

**b)** There are reports of men with painful erections occurring 1 to 3 days after beginning olanzapine. One was an African-American man with no previous symptoms of sexual dysfunction receiving olanzapine 15 mg nightly (Gordon & De Groot, 1999). The other was a 68-year old man with multiple sclerosis involving the spinal cord and a history of prostate surgery receiving olanzapine 5 mg daily. Both required shunt placement and their erectile function did not return (Heckers et al, 1998).

**c)** One report of an African-American man with a history of hypersexual behavior receiving olanzapine 10 to 15 milligrams (mg) daily. He complained of increased frequency and duration of erections (up to 2 hours). Within 1 week of olanzapine discontinuation, he reported a decrease in symptoms (Deirmenjian et al, 1998).

**3.3.15 Respiratory Effects**

**3.3.15.A Respiratory finding**

**1)** Summary

**a)** A 28-year-old male patient developed a PULMONARY EMBOLISM after beginning olanzapine therapy for the treatment of a psychotic disorder. Olanzapine therapy was initiated at 10 milligrams (mg)/day and gradually increased to 30 mg/day. Following 10 weeks of therapy, a pulmonary embolism was found on spiral computed tomography, which was performed after the patient complained of respiratory pain and experienced two episodes of hemoptysis. Olanzapine treatment was discontinued and the patient's symptoms resolved with anticoagulant therapy. Because tests for possible coagulation disorders did not reveal any underlying risks factors for this patient, olanzapine was believed to be the causal effect for the development of the pulmonary embolism (Waage & Gedde-Dahl, 2003).

**b)** The manufacturer reports that RHINITIS (7%), INCREASED COUGH (6%), PHARYNGITIS (4%), and DYSPNEA have been associated with olanzapine therapy (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a); (Beasley et al, 1996). ASPIRATION has also been associated with antipsychotic therapy. Two patients with Alzheimer's disease died of ASPIRATION PNEUMONIA while receiving olanzapine (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a).

**2)** Rhinitis, increased cough, pharyngitis, dyspnea, aspiration, and pulmonary embolism are reported with olanzapine administration.

### 3.3.16 Other

#### 3.3.16.A Summary

**1)** OTHER EFFECTS

**a)** In a large trial comparing haloperidol and olanzapine in schizophrenic patients, discontinuation of therapy due to adverse effects was required less often with olanzapine. Withdrawal syndrome has been reported with olanzapine therapy.

**2)** OTHER FINDINGS

**a)** In a large trial comparing haloperidol and olanzapine in schizophrenic patients (n=1,996), discontinuation of therapy due to adverse effects was required less often with olanzapine (3.6% versus 7.4% of patients) (Anon, 1995).

#### 3.3.16.B Death

**1)** Summary

**a)** The findings of one meta-analysis suggest that there may be a small increased risk of death associated with the use of atypical antipsychotic agents for the treatment of **dementia** in elderly patients. The study analysis (n=5110), including 15 randomized, double-blind, placebo-controlled, parallel group trials of antipsychotic use (ie, aripiprazole (n=3), olanzapine (n=5), quetiapine (n=3), risperidone (n=5)) in elderly patients (weighted mean age, 81.2 years) with **dementia**, found that death occurred more often in patients receiving atypical antipsychotic therapy as compared with placebo (118 (3.5%) vs 40 (2.3%), respectively). The overall odds ratio, as assessed by meta-analysis, for death in elderly patients receiving atypical antipsychotics as compared with placebo was 1.54 (95% CI= 1.06 to 2.23; p=0.02), and the risk difference was 0.01 (95% CI= 0.004 to 0.02; p=0.01). Overall, the relative risk associated with atypical antipsychotic use was 1.65 (95% CI= 1.19 to 2.29; p=0.003); however this increased risk was only identified when all drugs were pooled for analysis; meta-analyses of individual drugs did not show a statistically significant increased risk. A similar drop-out rate was observed between antipsychotic- and placebo-treated patients (32.2% vs 31.4%, respectively), with no significant difference in drop-outs found by meta-analysis (Schneider et al, 2005).

**b)** The results of a retrospective cohort study indicate that conventional antipsychotic agents are at least as likely as atypical antipsychotic agents to increase the risk of death among elderly patients 65 years of age or older. The study included 9,142 new users of conventional agents (mean age, 83.2 years) and 13,748 new users of atypical agents (mean age, 83.5 years). A higher adjusted relative risk

of death was associated with the use of conventional antipsychotics as compared with atypical antipsychotics at all timepoints studied after beginning therapy (within 180 days: RR, 1.37; 95% CI=1.27 to 1.49; less than 40 days: RR, 1.56; 95% CI=1.37 to 1.78; 40 to 79 days: RR, 1.37; 95% CI=1.19 to 1.59; 80 to 180 days: RR, 1.27; 95% CI=1.14 to 1.41). In addition, the adjusted risks of death observed in patients with **dementia** (RR, 1.29; 95% CI=1.15 to 1.45), without **dementia** (RR, 1.45; 95% CI=1.30 to 1.63), in a nursing home (RR, 1.26; 95% CI=1.08 to 1.47), or not in a nursing home (RR, 1.42; 95% CI=1.29 to 1.56) were also higher with the use of conventional antipsychotic therapy as compared with atypical antipsychotic use. This risk appeared to be dose-related and was greater with the use of higher dose (ie, greater than the median) conventional antipsychotics (RR, 1.73; 95% CI=1.57 to 1.90). Additional studies which specifically investigate the optimum care of elderly patients requiring antipsychotic therapy are needed so that appropriate guidance regarding therapeutic intervention can be provided (Wang et al, 2005).

**c)** A pooled analysis of five placebo-controlled trials revealed a significantly higher incidence of death in elderly patients with **dementia**- related psychosis who were treated with olanzapine as compared with placebo (3.5% vs 1.5%, respectively; p=0.024). Possible risk factors associated with increased mortality in this patient population include age greater than 80 years, sedation, concomitant use of benzodiazepines, and the presence of pulmonary conditions (ie, pneumonia, with or without aspiration). Mortality rate was not associated with duration of treatment and was not dose-related (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a; Pers Comm, 2004).

### 3.3.16.C Drug withdrawal

**1)** Summary

**a)** CASE REPORT - Within 3 days of stopping olanzapine therapy, a 33- year-old female developed myoclonic jerking, piloerection, headache, nightmares, depression, restlessness, and blurred vision. Because myoclonus is consistent with serotonergic hyperactivity, the authors suggested that the withdrawal represented a SEROTONERGIC REBOUND phenomena (Nayudu & Scheftner, 2000).

## 3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

**A)** Teratogenicity/Effects in Pregnancy

**1)** U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Zyprexa(R), 2000) (All Trimesters)

**a)** Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

**2)** Australian Drug Evaluation Committee's (ADEC) Category: B3 (Batagol, 1996)

**a)** Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

**3)** Crosses Placenta: Yes

**4)** Clinical Management

**a)** There is insufficient evidence to clearly establish the safety of olanzapine during pregnancy. However, given the likely morbidity and/or mortality associated with debilitating mental disorders during pregnancy, the benefits to the mother should be weighed against the potential risk to the fetus. Furthermore, limited data to date do not suggest an increased risk of major malformation (Ernst &

Goldberg, 2002; Goldstein et al, 2000); notably, schizophrenic women may have higher prevalence rates of social and lifestyle behaviors (e.g. smoking, alcohol and/or drug use, low socioeconomic status) associated with risky neonatal outcomes (Patton et al, 2002). Patients with histories of chronic psychosis or severe bipolar disorder should be maintained on medication therapy throughout gestation, as these patients and their fetuses represent a high risk group (Altshuler et al, 1996).

**5)** Literature Reports

**a)** Seven pregnancies occurred during clinical trials with olanzapine, which resulted in 2 normal births, 1 neonatal death due to cardiovascular defect, 3 therapeutic abortions and 1 spontaneous abortion (Prod Info Zyprexa(R), 2000). However, in 23 prospectively identified pregnancies, there was no increase in risk of spontaneous abortion, stillbirth, prematurity, or major malformation in those infants exposed to olanzapine in utero (Goldstein et al, 2000). Analysis of expanded data from this latter report produced similar conclusions; data included 96 pregnancies, among which 71.9% resulted in normal births, 12.5% in spontaneous abortions, 2.1% in premature deliveries, 3.1% in stillbirths, and 1% in major malformation (Ernst & Goldberg, 2002). The authors who relayed this written communication from the manufacturer stated that all of these occurrence rates were within the normal historical control rates. From an ongoing study to assess the fetal safety of atypical antipsychotics, interim results from 32 exposures to risperidone, olanzapine, or quetiapine had the following outcomes: 20 live births with no malformations, 3 spontaneous abortions, 2 stillbirths, and 7 therapeutic abortions (McKenna et al, 2003).

**b)** Occasional spontaneous case reports of in utero exposure to olanzapine have produced viable newborns, although long-term effects remain to be established (Mendhekar et al, 2002; Nagy et al, 2001; Littrell et al, 2000; Kirchheiner et al, 2000). One isolated case of maternal use of up to 20 mg of olanzapine and 2 mg of trihexyphenidyl daily from the 23rd week of gestation until 10 days prior to delivery has been reported. In this case, a healthy baby was delivered with Apgar scores of 8-10 at 1 minute, and 9-10 at 5 minutes; at 3 months of age, the infant showed age-appropriate milestones (Mendhekar et al, 2002). A single case of olanzapine 10 mg per day exposure from the 18th week of pregnancy through delivery and during breastfeeding also exists. Delivery was uncomplicated and, despite suspicious motor development at 7 months of age, the infant showed no abnormal findings at 11 months of age (Kirchheiner et al, 2000). In both of these cases, olanzapine exposure did not occur during first trimester, a period where teratogenic effects would be more likely.

**B)** Breastfeeding

**1)** Thomson Lactation Rating: Infant risk cannot be ruled out.

**a)** Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

**2)** Clinical Management

**a)** Limited data suggest that olanzapine is excreted into human breast milk; the potential for adverse effects in the nursing infant from exposure to the drug are unknown (Prod Info Zyprexa(R), 2003; Croke et al, 2002). The manufacturer advises against breastfeeding in women who use olanzapine (Prod Info Zyprexa(R), 2003). However, occasional and sporadic case reports have substantiated a lack of adverse effects to the nursing infant.

**3)** Literature Reports

**a)** Cases of olanzapine exposure via breast milk have been reported in the literature; the limited data fail to affirm or eliminate the potential for adverse effects in the nursing infant. One case describes an infant exposed in utero to olanzapine (maternal dose 5 mg/day) who was born with cardiomegaly, jaundice, somnolence, and a heart murmur (Goldstein et al, 2000a). However, jaundice and sedation continued despite the initiation of bottle-feeding on day seven of life. In the same report, a second infant exposed at two months of age (maternal dose 10 mg/day) had no adverse effects. In yet another infant born to a mother who had taken olanzapine 10mg daily throughout her pregnancy and during breastfeeding, infant plasma levels were undetectable (less than 2 ng/mL) despite maternal steady-state trough levels of 32.8 to 39.5 ng/mL (Kirchheiner et al, 2000a). In 7 nursing mothers receiving 5 to 20 milligrams/day of olanzapine, the median infant dose ingested through breast milk was approximately 1% (Gardiner et al, 2003).

**b)** Using milk and plasma samples from five nursing mothers who took olanzapine 2.5 mg to 10 mg

daily, milk-to-plasma ratios ranged from 0.2 to 0.84 (Croke et al, 2002). This compared to a theoretical value of 0.38 that was determined using the known pharmacokinetic parameters of the drug. Based on average milk consumption of 0.15 L/kg/day and assuming 100% bioavailability, relative infant dose was estimated to be 0% to 2.5% of the weight-adjusted maternal dose.

**4)** Drug Levels in Breastmilk

**a)** Parent Drug

**1)** Milk to Maternal Plasma Ratio

**a)** 0.2 to 0.84 (mean 0.46) (Buist & A, 2001; Croke et al, 2002)

## 3.5 Drug Interactions

### 3.5.1 Drug-Drug Combinations

#### 3.5.1.A Activated Charcoal

**1)** Interaction Effect: decreased bioavailability of olanzapine

**2)** Summary: Activated charcoal reduces the maximum concentration and area under the concentration-time curve (AUC) by approximately 60% (Prod Info Zyprexa(R), 1999b). This drug interaction may make activated charcoal useful in cases of olanzapine overdose.

**3)** Severity: minor

**4)** Onset: rapid

**5)** Substantiation: theoretical

**6)** Clinical Management: Do not administer activated charcoal and olanzapine concomitantly.

**7)** Probable Mechanism: binding of olanzapine in the gut

#### 3.5.1.B Belladonna

**1)** Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, excessive sedation, blurred vision)

**2)** Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with olanzapine. Belladonna contains L-hyoscyamine, atropine, and scopolamine with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with olanzapine is unknown. Caution is advised.

**3)** Severity: minor

**4)** Onset: rapid

**5)** Substantiation: theoretical

**6)** Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, tachycardia, decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, paralytic ileus, confusion, psychoses, agitation, delusions, delirium, and paranoia may be encountered as well as tachycardia, dysrhythmia, and hypertension. In severe cases, immediate medical attention should be obtained.

**7)** Probable Mechanism: additive anticholinergic effect

#### 3.5.1.C Belladonna Alkaloids

**1)** Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, excessive sedation, blurred vision)

**2)** Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with olanzapine. Belladonna contains L-hyoscyamine, atropine, and scopolamine with a total alkaloid content of at least 0.3% in the leaves and

0.5% in the roots (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with olanzapine is unknown. Caution is advised.
**3)** Severity: minor
**4)** Onset: rapid
**5)** Substantiation: theoretical
**6)** Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, tachycardia, decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, paralytic ileus, confusion, psychoses, agitation, delusions, delirium, and paranoia may be encountered as well as tachycardia, dysrhythmia, and hypertension. In severe cases, immediate medical attention should be obtained.
**7)** Probable Mechanism: additive anticholinergic effect

**3.5.1.D Betel Nut**

**1)** Interaction Effect: increased extrapyramidal side effects of olanzapine (difficulty with movement or abnormal movement of muscles)
**2)** Summary: Case reports have described increased extrapyramidal side effects when betel nut was chewed by patients taking fluphenazine and fluphenthixol for schizophrenia (Deahl, 1989a). The extrapyramidal effects were not improved with anticholinergic therapy with procyclidine, and resolved with betel nut discontinuation (Deahl, 1989a). A similar effect may occur if betel nut is chewed with concomitant olanzapine therapy. The cholinergic activity of betel nut has been attributed to the arecoline content. When given with peripheral anticholinergics, arecoline increased the heart rate due to central muscarinic agonist activity (Nutt et al, 1978a). Case reports suggest the onset of betel nut activity to be within 3 weeks with resolution within 4 to 7 days after discontinuation (Deahl, 1989a).
**3)** Severity: moderate
**4)** Onset: delayed
**5)** Substantiation: probable
**6)** Clinical Management: It is unclear to what extent the cholinergic effect of betel nut may increase the incidence of extrapyramidal side effects of olanzapine, especially if patients are treated with anticholinergic agents to control these side effects. Deterioration in symptoms of patients with Parkinson's disease or other extrapyramidal movement disorders may be expected. Persons who have been chewing betel nut have a characteristic red stain on the teeth which may help the clinician discover betel nut use.
**7)** Probable Mechanism: cholinergic effect of betel nut
**8)** Literature Reports
**a)** Within 3 weeks of initiating betel nut chewing, a 51-year-old Indian man experienced marked rigidity, bradykinesia, and jaw tremor. This patient had been stabilized for the previous 2 years on fluphenazine decanoate depot 50 milligrams (mg) every 3 weeks for schizophrenia and procyclidine 5 mg twice daily for a mild Parkinsonian tremor. Within one week of discontinuation of betel nut chewing, the patient's condition returned to baseline. This report appears to demonstrate decreased anticholinergic effects of procyclidine when coadministered with betel nut (Deahl, 1989).
**b)** Following betel nut ingestion, a 45-year-old Indian man developed akathisia, tremor and stiffness which was not affected by dosage escalations of up to 20 mg daily of procyclidine. This patient had been previously stabilized on fluphenthixol 60 mg depot every two weeks for the previous year for schizoaffective disorder without extrapyramidal side effects. His symptoms resolved over 4 days after discontinuing betel nut. It appears that the anticholinergic effects of procyclidine were diminished when betel nut was chewed concomitantly (Deahl, 1989).
**c)** High doses (5 mg, 10 mg, and 20 mg) of subcutaneous (SC) arecoline given one hour after SC administration of 0.5 mg of the peripheral anticholinergic agent methscopolamine increased the heart rate and blood pressure of six patients with Huntington's disease. Significant increases in blood pressure occurred at doses of 5 mg, 10 mg (p less than 0.01) and 20 mg (p less than 0.05). Heart rate increased at doses of 5 mg and 20 mg (p less than 0.01), and 10 mg (p less than 0.05). Subjective

effects in some patients included tremor, flushing or pallor at the time of peak drug effect and nausea, weakness, and mental changes at the higher doses. No peripheral cholinergic effects were noted. The results indicated a central muscarinic effect for arecoline (Nutt et al, 1978).

**d)** A low dose (0.5 mg) of arecoline given intravenously 3 minutes after the peripheral anticholinergic agent glycopyrrolate 0.15 mg to 8 patients with major depressive disorder increased their heart rates. The peak heart rate increase in a non-REM portion of the sleep cycle during the 10 minute post-infusion period was 6.75 +/- 12.9 beats per minute for placebo and 25 +/- 10.3 beats per minute for arecoline. The peak heart rates all began 1 to 8 minutes after the arecoline infusion, and the mean heart rate was significantly elevated over placebo from 2 to 10 minutes after arecoline infusion (p less than 0.05) (Abramson et al, 1985).

**e)** Though chewing betel nut alone does not significantly increase catecholamine levels, a popular betel nut preparation does. Six to eight minutes after chewing betel nut, 4 subjects had only a moderate increase in plasma noradrenaline from 266.2 +/- 105.7 picograms/milliliter (pg/mL) to 313.7 +/- 92.9 pg/mL (p equal to 0.0607). Combining betel nut with lime, catechu and Piper betel flower as is commonly done caused significant elevation of norepinephrine in nine subjects from 292.2 +/- 59.5 pg/mL to 375.1 +/- 130.0 pg/mL (p equal to 0.0244) and epinephrine from 62.5 +/- 23.9 pg/mL to 102.2 +/- 45.0 pg/mL (p equal to 0.0226). In this group dopamine was also elevated in 8 of 9 subjects, but the mean was not significant (Chu, 1995).

### 3.5.1.E Carbamazepine

**1)** Interaction Effect: reduced olanzapine efficacy

**2)** Summary: Carbamazepine induces CYP1A2 mediated oxidation. Concomitant administration of olanzapine and carbamazepine 200 mg twice daily increased the clearance of olanzapine by 50% (Prod Info Zyprexa(R), 1999a). Higher daily doses of carbamazepine may cause an even greater effect on olanzapine clearance. In a study of 11 healthy volunteers, concurrent administration of olanzapine and carbamazepine resulted in a 46% increase in olanzapine clearance (Lucas et al, 1998). Because patients respond to a relatively wide range of olanzapine serum concentrations, close clinical observation of symptom patterns and changes is necessary whenever carbamazepine is added to or withdrawn from olanzapine therapy. The need for olanzapine dose adjustments will most likely be highly patient specific (Licht et al, 2000a).

**3)** Severity: moderate

**4)** Onset: rapid

**5)** Substantiation: probable

**6)** Clinical Management: Monitor patients for olanzapine efficacy. Doses of olanzapine may need to be adjusted when given concomitantly with carbamazepine.

**7)** Probable Mechanism: induction of cytochrome P450 1A2-mediated olanzapine metabolism

**8)** Literature Reports

**a)** A 23-year-old paranoid schizophrenic female was admitted to the hospital for treatment of hallucinations and delusions. Her only medication on admission was perphenazine 12 mg daily, but carbamazepine 600 mg daily was initiated for aggressive outbursts. Perphenazine was replaced by risperidone 6 mg daily due to akathisia, rigidity, and tremor, but risperidone was also discontinued due to extrapyramidal side effects. Olanzapine 15 mg daily was started and her psychiatric symptoms improved over the next three weeks. Because her aggressive outbursts were still present, carbamazepine was discontinued due to lack of efficacy. She had received cotherapy with olanzapine 15 mg daily and carbamazepine 600 mg daily for three consecutive weeks. The day prior to carbamazepine discontinuation, the patient's olanzapine serum concentration was measured at 21 ng/mL. Over the next few weeks, her olanzapine concentration increased by 114% to 45 ng/mL. The dose of olanzapine was decreased to 10 mg daily and a corresponding fall in the olanzapine level occurred. This case report suggests that carbamazepine induces the metabolism of olanzapine, most likely through the cytochrome P450 1A2 enzyme system (Licht et al, 2000).

### 3.5.1.F Ciprofloxacin

**1)** Interaction Effect: an increased risk of olanzapine toxicity (increased sedation, orthostatic hypotension)
**2)** Summary: Ciprofloxacin was suspected of inhibiting the metabolism of olanzapine in a 54-year-old female receiving concurrent therapy. Cytochrome P450 1A2 (CYP1A2) has been shown in vitro to be responsible for the formation of some of the metabolites of olanzapine, and ciprofloxacin is a known potent inhibitor of CYP1A2. Although olanzapine has a wide therapeutic range and a correlation between plasma concentrations and adverse effects has not been established, this interaction may be clinically significant (Markowitz & DeVane, 1999a).
**3)** Severity: moderate
**4)** Onset: delayed
**5)** Substantiation: probable
**6)** Clinical Management: Patients receiving olanzapine and ciprofloxacin concurrently should be monitored for increased olanzapine adverse effects, such as increased sedation and orthostatic hypotension.
**7)** Probable Mechanism: inhibition by ciprofloxacin of cytochrome P450 1A2-mediated olanzapine metabolism
**8)** Literature Reports
**a)** A 54-year-old female was admitted to the hospital with suicidal ideation and lacerations to her wrists. Medication prior to admission included olanzapine 10 mg at bedtime, nefazodone 100 mg twice daily, atenolol 25 mg daily, levothyroxine 0.25 mg daily, and phenytoin 100 mg twice daily. Nefazodone was tapered off prior to electroconvulsive therapy, and ciprofloxacin 250 mg twice daily for seven days was initiated for a suspected urinary tract infection. Immediately before her last dose of ciprofloxacin, the plasma olanzapine concentration was 32.6 ng/mL. Three days after ciprofloxacin was discontinued, her olanzapine concentration had decreased by more than 50% to 14.6 ng/mL. Although this patient did not experience any adverse effects from her increased olanzapine level, higher doses of ciprofloxacin could potentially cause more inhibition of olanzapine metabolism (Markowitz & DeVane, 1999).

### 3.5.1.G Clomipramine

**1)** Interaction Effect: an increased risk of seizures
**2)** Summary: Psychotropic drugs have been shown to reduce the seizure threshold. A case report describes a patient without an underlying seizure disorder who received treatment with olanzapine and clomipramine concomitantly. This combination resulted in seizures which were repeated upon rechallenge with olanzapine and clomipramine. It is advised to use caution when administering olanzapine concomitantly with clomipramine, or any agent known to reduce seizure threshold (Deshauer et al, 2000a).
**3)** Severity: major
**4)** Onset: delayed
**5)** Substantiation: probable
**6)** Clinical Management: It is advised to use caution when administering olanzapine concomitantly with clomipramine, or other agents known to lower the seizure threshold.
**7)** Probable Mechanism: unknown
**8)** Literature Reports
**a)** A 34-year-old male with schizophrenia and obsessive-compulsive disorder (OCD) without any underlying seizure disorder, presented for treatment following long-term noncompliance. Inpatient olanzapine treatment (20 mg/day) was initiated and positive psychotic symptoms subsequently resolved. Patient was discharged and readmitted because of inability to control symptoms. Clomipramine 250 mg per day was initiated. Within a week, dizziness and myoclonic jerks were reported which quickly progressed to general motor seizures and postictal somnolence (without incontinence). Spike waves and paroxysmal slowing on the EEG was consistent with seizure activity. Clomipramine and olanzapine were subsequently withheld, and the seizures were controlled with

diazepam 30 mg per day for three days. This pattern repeated upon re-challenge with the combination of olanzapine and clomipramine. Presumably from the temporal relationship between clomipramine and olanzapine administration and seizure manifestation, it can be suspected that this adverse event is due to an interaction between these two drugs. Clomipramine and olanzapine are both metabolized by the cytochrome P450 isoenzymes 1A2 and 2D6. One theory is that coadministration may result in elevated levels of both compounds. Although the mechanism by which this interaction occurs is not yet known, it is advised to use caution when administering olanzapine concomitantly with clomipramine, or other agents known to lower the seizure threshold (Deshauer et al, 2000).

**3.5.1.H Dehydroepiandrosterone**

**1)** Interaction Effect: reduced effectiveness of olanzapine
**2)** Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive for optimal treatment of patients with psychosis (Howard, 1992a). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992a). Patients being treated with olanzapine should avoid DHEA supplementation.
**3)** Severity: moderate
**4)** Onset: delayed
**5)** Substantiation: theoretical
**6)** Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and olanzapine. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
**7)** Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to olanzapine
**8)** Literature Reports

**a)** A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992).

**b)** A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications". DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992).

**3.5.1.I Eszopiclone**

**1)** Interaction Effect: decreased psychomotor function
**2)** Summary: Coadministration of 3 mg eszopiclone and 10 mg olanzapine resulted in the pharmacodynamic manifestation of decreased Digital Symbol Substitution Test scores, a measurement of psychomotor function. No pharmacokinetic interactions were observed. Monitor patients for decreased psychomotor function (Prod Info LUNESTA(TM), 2004).
**3)** Severity: minor
**4)** Onset: unspecified
**5)** Substantiation: theoretical
**6)** Clinical Management: Monitor patients for decreased psychomotor function. Adjust dose accordingly or consider alternative therapy for insomnia.
**7)** Probable Mechanism: unknown

**3.5.1.J Fluvoxamine**

**1)** Interaction Effect: an increased risk of olanzapine adverse effects
**2)** Summary: Fluvoxamine inhibits cytochrome P450 1A2 enzymes and may inhibit olanzapine elimination (Prod Info Zyprexa(R), 1999). The clinical significance of this interaction is unknown since olanzapine is metabolized by multiple enzyme systems.
**3)** Severity: moderate
**4)** Onset: delayed
**5)** Substantiation: probable
**6)** Clinical Management: Monitor patients for excessive olanzapine adverse effects (orthostatic hypotension, tachycardia, transaminase elevations, seizures).
**7)** Probable Mechanism: inhibition of olanzapine elimination
**8)** Literature Reports
**a)** A patient experienced elevated olanzapine plasma levels during coadministration of fluvoxamine. The patient was taking fluvoxamine and olanzapine for several months for schizophrenia and secondary depression. She appeared to move rigidly, had a slight tremor of both hands and mydriasis. Olanzapine concentration was 120 mcg/L and fluvoxamine concentration was 70 mcg/L. Olanzapine was decreased in increments from 15 mg/day to 5 mg/day. Fourteen days after the last decrease in dose, olanzapine plasma levels were 38 mcg/L. Tremor and rigidity disappeared, however, mydriasis persisted. Fluvoxamine was replaced by paroxetine which resulted in paroxetine concentration of 0.027 mg/L and olanzapine concentration of 22 mcg/L (de Jong et al, 2001).
**b)** Addition of fluvoxamine to olanzapine therapy may result in olanzapine-induced side effects or intoxication. Eight chronic schizophrenic patients were being treated for not less than 3 months with 10-20 mg/day of olanzapine. The dose of olanzapine was unchanged for not less than 8 weeks prior to the study and remained stable throughout the study period. Fluvoxamine 100 mg/day was added to olanzapine treatment at the start of the study (week 0) and continued for 8 weeks. Olanzapine concentrations increased during fluvoxamine treatment 1.58-fold from week 0 to week 1, 1.42-fold from week 0 to week 4, and 1.81-fold from week 0 to week 8. Percentage change from week 0 to week 8 ranged from 12% to 112%. Mean concentrations of the N-demethylated metabolite were not significantly changed. Even though all eight patients had higher olanzapine blood serum concentrations on week 8 than on week 1, the ratio of increase of olanzapine blood serum concentrations from week 0 to week 8 did not correlate significantly with fluvoxamine serum levels (p greater than 0.05). This study confirmed that the addition of fluvoxamine to a stable dose of olanzapine increased olanzapine concentrations in the blood serum. Combined olanzapine and fluvoxamine should be used cautiously and controlled clinically and by therapeutic drug monitoring to avoid olanzapine-induced side effects or intoxication (Hiemke et al, 2002).

**3.5.1.K Haloperidol**

**1)** Interaction Effect: an increased risk of parkinsonism (cogwheeling rigidity, unstable gait)
**2)** Summary: A patient receiving haloperidol experienced extreme parkinsonism following the addition

of olanzapine therapy. Possible explanations include a pharmacokinetic interaction between olanzapine, a weak cytochrome P450 2D6 (CYP2D6) inhibitor, and haloperidol, a CYP2D6 substrate. Pharmacodynamically, the small amount of dopamine (D2) blockade from olanzapine may have been enough to increase the patient's parkinsonism (Gomberg, 1999a).
**3)** Severity: moderate
**4)** Onset: delayed
**5)** Substantiation: probable
**6)** Clinical Management: Patients should be closely monitored for signs and symptoms of increased parkinsonian adverse effects when olanzapine is added to haloperidol therapy. Doses of haloperidol may need to be decreased.
**7)** Probable Mechanism: competitive inhibition of cytochrome P450 2D6-mediated haloperidol metabolism; increased dopamine D2 blockade
**8)** Literature Reports
**a)** A 67-year-old hospitalized male with bipolar disorder who had stopped taking his medications was restarted on haloperidol 10 mg nightly, benztropine 1 mg nightly, and valproate 750 mg twice daily. He had been experiencing some mild parkinsonian symptoms at baseline, but these symptoms did not worsen when haloperidol was reinstituted. Following stabilization on this regimen, it was decided to change his antipsychotic medication to olanzapine to minimize any parkinsonism that was a result of his medications. While tapering the haloperidol and initiating olanzapine, the patient experienced extreme parkinsonism that resulted in an inability to walk. His mental status remained unchanged. Haloperidol was discontinued on day 7 of combination therapy, and two days later the patient's parkinsonism side effects had resolved back to baseline. Benztropine was then discontinued, and the parkinsonian symptoms did not reoccur while on olanzapine (Gomberg, 1999).

**3.5.1.L Levodopa**

**1)** Interaction Effect: decreased levodopa effectiveness
**2)** Summary: Concurrent use of olanzapine may antagonize the pharmacological effects of levodopa (Prod Info Zyprexa(R), 1999c). The clinical significance of this interaction is unknown.
**3)** Severity: moderate
**4)** Onset: rapid
**5)** Substantiation: theoretical
**6)** Clinical Management: Monitor patients for levodopa efficacy.
**7)** Probable Mechanism: pharmacological antagonism

**3.5.1.M Levomethadyl**

**1)** Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
**2)** Summary: Any drug known to have the potential to prolong the QT interval should not be used with levomethadyl. Possible pharmacodynamic interactions can occur between levomethadyl and potentially arrhythmogenic agents such as olanzapine that prolong the QT interval (Prod Info Orlaam(R), 2001).
**3)** Severity: contraindicated
**4)** Onset: delayed
**5)** Substantiation: theoretical
**6)** Clinical Management: Levomethadyl is contraindicated in patients being treated with olanzapine as it may precipitate QT prolongation and interact with levomethadyl.
**7)** Probable Mechanism: additive cardiac effects

**3.5.1.N Lithium**

**1)** Interaction Effect: weakness, dyskinesias, increased extrapyramidal symptoms, encephalopathy, and

brain damage

**2)** Summary: An encephalopathic syndrome followed by irreversible brain damage has occurred in a few patients treated with lithium plus haloperidol. A causal relationship between these events and the concomitant administration of haloperidol and lithium has not been established (Prod Info Lithium Carbonate, 2002). Coadministration of lithium and a number of antipsychotic drugs has caused a wide variety of encephalopathic symptoms, brain damage, extrapyramidal symptoms, and dyskinesias in isolated case reports. In most cases, these effects have occurred with therapeutic lithium levels (Amdisen, 1982; Prakash, 1982; Addonizio et al, 1988a). However, many series and trials have reported using such combinations with no severe adverse consequences (Goldney & Spence, 1986). The mechanism is not fully understood, but chronic lithium treatment decreases neostriatal dopaminergic activity, probably through a direct action on the G protein and the capacity of the G proteins, once activated, to stimulate adenyl cyclase (Carli et al, 1994). Hyperglycemic reactions have also occurred during combined phenothiazine and lithium use (Zall et al, 1968).

**3)** Severity: major

**4)** Onset: delayed

**5)** Substantiation: probable

**6)** Clinical Management: Monitor patients closely for any signs of toxicity or extrapyramidal symptoms, especially if high doses of antipsychotic drugs and lithium are used. Serum lithium levels should be monitored periodically. Some clinicians advocate maintaining levels in the low therapeutic range.

**7)** Probable Mechanism: unknown

**8)** Literature Reports

**a)** Concomitant haloperidol and lithium therapy has resulted in symptoms of encephalopathy, confusion, extrapyramidal symptoms, and fever in several patients with mania (Cohen & Cohen, 1974; Loudon & Waring, 1976; Thomas, 1979). Irreversible neurological injuries have been reported (Sandyk & Hurwitz, 1983; Keitner & Rahman, 1984).

**b)** Seizures, encephalopathy, delirium, and abnormal EEG occurred in four patients during combined lithium and thioridazine therapy (Spring, 1979). Serum lithium levels were below 1 mEq/L at the time of the toxic reaction in all cases. All patients had previously tolerated lithium in combination with another phenothiazine. Three of these patients developed symptoms within eight days of initiating combination therapy.

**c)** The addition of lithium to neuroleptic therapy exacerbated extrapyramidal symptoms (EPS) in a small study (Addonizio et al, 1988). The patients had received at least five days of treatment with either oral thiothixene, haloperidol, or fluphenazine in mean doses of 607.5 chlorpromazine equivalents prior to initiation of the lithium and were experiencing drug-induced extrapyramidal symptoms. Oral lithium was added when clinically indicated in sufficient doses to achieve a therapeutic serum concentration. The maximum levels attained were 0.65 to 1.27 mEq/L. The EPS ratings increased in all ten patients following the addition of lithium. However, only three patients developed marked symptoms and no patient developed lithium toxicity. Significantly increased symptoms included gait, shoulder shaking, elbow rigidity, and tremor.

**d)** Ten patients treated with clozapine and lithium were studied (Blake et al, 1992). Of the ten patients, four experienced significant neurologic effects, including jerking of limbs, facial spasms and tics, tremor of hands and arms, tongue twitching, and stumbling gait. One of these also experienced delirium. These effects reversed when lithium was discontinued or given at a lower dose. On rechallenge, one of two patients suffered recurrence of symptoms. By keeping serum lithium no greater than 0.5 mEq/L, clozapine could be safely coadministered.

**e)** Chlorpromazine serum levels can be significantly reduced in the presence of lithium treatment. If used concurrently, abrupt cessation of lithium may result in rebound elevation of chlorpromazine levels, resulting in chlorpromazine toxicity. In patients on a lithium-chlorpromazine combination, abrupt withdrawal of the lithium may precipitate chlorpromazinecardiotoxicity. In this report, such toxicity was manifested as sudden ventricular fibrillation associated with prolongation of the QTc interval. Hypotension and EPS are also possible in this situation (Stevenson et al, 1989).

**f)** However, other data do not support that such adverse events are frequent or indeed causally related to combination therapy. Combination of dopamine antagonist antipsychotic drugs and lithium have

been used successfully in many patients with manic-depressive illness. It has been proposed that the interaction may only become significant with very high doses of one or both drugs or with failure to discontinue dosing in the presence of toxic symptoms (Miller & Menninger, 1987).
**g)** A 69-year-old patient with oxygen-dependent chronic obstructive pulmonary disorder and a 25-year history of bipolar disorder was started on risperidone 3 mg for the treatment of new-onset auditory and visual hallucinations. She had also been maintained on a regimen of lithium (450 mg daily) for more than 10 years. In addition, she was given amantadine (100 mg twice daily) for tremor. Three weeks after the start of risperidone, the patient experienced a decline in mental status in addition to dizziness, worsening tremors, nausea and vomiting, polyuria, depression, and visual and auditory hallucinations. She was then admitted to the hospital for delirium. Her lithium serum level was 1.36 mEq/L at the time of the admission. All medications were discontinued. Although her lithium level decreased to 0.41 mEq/L, she continued to experience profound delirium, tremors, lethargy, and hallucinations for almost one week. After she started to respond to commands, she was restarted on lithium (300 mg at bedtime) because of the onset of mild hypomania. Five days later, she was discharged with a regimen of lithium and low-dose lorazepam for treatment of insomnia. It is suggested that delirium could have been caused by the concurrent use of lithium and risperidone. Other factors could also have caused delirium, such as the patient's serum lithium level and the underlying pulmonary pathology. In addition, amantadine, which facilitates the release of presynaptic dopamine and has a mild anticholinergic effect, may have contributed (Chen & Cardasis, 1996).

### 3.5.1.O Phenylalanine

**1)** Interaction Effect: increased incidence of tardive dyskinesia
**2)** Summary: Taking phenylalanine concomitantly with certain neuroleptic drugs may exacerbate tardive dyskinesia (Gardos et al, 1992a). Abnormal phenylalanine metabolism in certain patients may lead to phenylalanine accumulation in the brain and in turn, reduced brain availability of other large neutral amino acids. This may interfere with the synthesis of catecholamines (Gardos et al, 1992a).
**3)** Severity: moderate
**4)** Onset: rapid
**5)** Substantiation: theoretical
**6)** Clinical Management: Caution is advised if phenylalanine is administered with a neuroleptic agent. Monitor the patient closely for signs of tardive dyskinesia.
**7)** Probable Mechanism: reduced brain availability of other large neutral amino acids and interference with catecholamine synthesis
**8)** Literature Reports
**a)** Phenylalanine tended to increase the incidence of tardive dyskinesia in patients taking neuroleptics in an open study. Three groups of patients were studied: (1) patients with unipolar depression with tardive dyskinesia (n=11), (2) patients with no tardive dyskinesia with current or past exposure to greater than or equal to 100 milligrams (mg) of a chlorpromazine equivalent for at least 3 months (n=10), and (3) patients with no tardive dyskinesia not previously exposed to a neuroleptic drug (n=10). Neuroleptic agents were taken during the study by 6 patients in group 1, and 5 patients in group 2. Patients received powdered phenylalanine 100 mg/kilogram dissolved in orange juice after an overnight fast. Blood samples were obtained just prior to phenylalanine administration and 2 hours after administration. Three patients in group 1 (with tardive dyskinesia) had the highest postloading phenylalanine plasma levels, this group as a whole had higher (though nonsignificant) mean phenylalanine levels than the other groups. Tardive dyskinesia score (measured using the Abnormal Involuntary Movements Scale (AIMS)) nonsignificantly increased in group 1. Postloading phenylalanine level and postloading AIMS scores were significantly positively correlated in group 1 (rs=0.347, p less than 0.05; Spearman correlation coefficient 0.543, p less than 0.05). Postloading phenylalanine level and baseline AIMS scores demonstrated a trend toward correlation (rs=0.246, p=0.092; Spearman correlation coefficient 0.679, p less than 0.05). In all patients, phenylalanine loading increased plasma phenylalanine levels approximately eight-fold, and plasma tyrosine increased 2.5 times as a result of conversion of phenylalanine to tyrosine. Plasma levels of competing large

neutral amino acids such as tryptophan decreased slightly (Gardos et al, 1992).

**3.5.1.P Ritonavir**

**1)** Interaction Effect: reduced olanzapine effectiveness
**2)** Summary: An open-label study involving 14 healthy volunteers revealed a significant alteration in pharmacokinetic parameters and a reduction in systemic exposure of olanzapine when administered in the presence of ritonavir. Baseline blood samples were drawn prior to each volunteer receiving one olanzapine 10 mg tablet. Venous blood samples were then obtained at specified times. After a 14-day washout period, subjects received ritonavir 300 mg BID for 3 days, then 400 mg BID for 4 days, then 500 mg BID for 4 days. Blood samples were again drawn at specified times. Once all samples were analyzed the results were as follows: Statistically significant reductions in the mean olanzapine area under the plasma concentration-time curve (AUC) by 53% (501 (ng)hr/mL to 235 (ng)hr/mL) (p less than 0.001); the half-life by 50% (from 32 hr to 16 hr) (p less than 0.00001) and the peak plasma concentration by 40% (from 15 ng/mL to 9 ng/mL) (p less than 0.002). The oral clearance of olanzapine increased by 115% (from 20 L/hr to 43 L/hr) (p less than 0.001). Because olanzapine is usually well-tolerated and a clear relationship between plasma concentrations and toxicity has not been defined, the clinical significance of this interaction needs further study (Penzak et al, 2002).
**3)** Severity: moderate
**4)** Onset: delayed
**5)** Substantiation: theoretical
**6)** Clinical Management: Monitor patients for olanzapine efficacy. Doses of olanzapine may need to be adjusted when given concomitantly with ritonavir. Patients stabilized on olanzapine and ritonavir, who have their ritonavir discontinued, should have be monitored closely for new effects resulting from increased systemic exposure to olanzapine.
**7)** Probable Mechanism: induction or CYP1A2- and glucuronosyl transferase-mediated metabolism of olanzapine by ritonavir

**3.5.1.Q St John's Wort**

**1)** Interaction Effect: reduced olanzapine efficacy
**2)** Summary: This interaction is based on in vitro information that St. John's Wort induced CYP1A2 enzymes, and a case report of a patient experiencing reduced blood theophylline concentrations and loss of efficacy (Nebel et al, 1999). Since olanzapine is metabolized by CYP1A2 enzymes, like theophylline, olanzapine may be similarly affected. If St. John's Wort and olanzapine are taken together, their dosages should be consistently administered, recognizing that increased dosages of olanzapine may be required. Discontinuation of St. John's Wort should be done carefully as side effects of olanzapine may increase and dose reduction may be required.
**3)** Severity: moderate
**4)** Onset: delayed
**5)** Substantiation: theoretical
**6)** Clinical Management: Avoid concomitant use of olanzapine with St. John's Wort. If patients elect to remain on St. John's Wort, they should maintain consistent dosing. Olanzapine dosage may need to be increased. Patients should not discontinue St. John's Wort without first consulting their clinician, as downward adjustments in olanzapine dose may be necessary as well as monitoring for increased side effects of olanzapine (e.g. somnolence, nausea, constipation, dry mouth, asthenia).
**7)** Probable Mechanism: induction of cytochrome P450 1A2 enzymes by St. John's Wort

**3.5.2 Drug-Food Combinations**

**3.5.2.A Ethanol**

**1)** Interaction Effect: excessive central nervous system depression
**2)** Summary: Coadministration of olanzapine and ethanol will potentiate the orthostatic hypotension observed with olanzapine alone. Although a single dose of ethanol (45 mg/70 kg) had no effect on olanzapine pharmacokinetics, these drugs should not be taken concomitantly due to the central nervous system depressive effects of both drugs (Prod Info Zyprexa(R), 1999d).
**3)** Severity: moderate
**4)** Onset: rapid
**5)** Substantiation: theoretical
**6)** Clinical Management: Concurrent use of olanzapine and ethanol should be avoided if at all possible. If these two are taken in combination, extreme caution should be used.
**7)** Probable Mechanism: additive central nervous system depression

## 4.0 Clinical Applications

Monitoring Parameters
Patient Instructions
Place In Therapy
Mechanism of Action / Pharmacology
Therapeutic Uses
Comparative Efficacy / Evaluation With Other Therapies

### 4.1 Monitoring Parameters

**A)** Therapeutic
**1)** Physical Findings
**a)** Improvement of schizophrenic symptoms on standard examination/testing
**1)** Positive symptoms (distortion of normal function) include hallucinations, irritability, delusions, incoherent speech, suspiciousness
**2)** Negative symptoms (loss or diminution of function) include blunted affect, emotional or social withdrawal, poverty of speech content, lack of initiative
**B)** Toxic
**1)** Laboratory Parameters
**a)** Liver function tests periodically during therapy.
**b)** White blood count.
**2)** Physical Findings
**a)** Examination/questioning to detect extrapyramidal effects (eg, continuous pacing, restlessness, fine tremor, abnormal posturing, spasticity, hypertonus)
**b)** Body weight, temperature, and systolic/diastolic pressure periodically during therapy
**c)** Monitor for orthostatic hypotension prior to the administration of repeated intramuscular doses of olanzapine (Prod Info Zyprexa(R) IntraMuscular, 2004).
**d)** Monitor patients with an established diagnosis of diabetes mellitus for worsening of glucose control during treatment with an atypical antipsychotic. Patients with risk factors for diabetes mellitus (ie, obesity, family history of diabetes) who are beginning treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically throughout treatment (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a).
**e)** Monitor patients for signs and symptoms of hyperglycemia (ie, polydipsia, polyuria, polyphagia, and weakness). Patients who exhibit symptoms of hyperglycemia during atypical antipsychotic treatment should undergo fasting blood glucose testing. In some instances, hyperglycemia has resolved when the

atypical antipsychotic was stopped; however, some patient required ongoing anti- diabetic treatment despite discontinuation of the suspect medication (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a).

**4.2 Patient Instructions**

**A)** OLANZAPINE (By mouth)
Olanzapine

Treats psychiatric (mental) disorders, including schizophrenia and some symptoms of bipolar I disorder.

When This Medicine Should Not Be Used:
You should not use this medication if you have ever had an allergic reaction to olanzapine.

How to Use This Medicine:
Tablet, Dissolving Tablet
Your doctor will tell you how much of this medicine to use and how often. Do not use more medicine or use it more often than your doctor tells you to.
You may take this medicine with or without food.
If you are using the make sure your hands are dry before you handle the tablet. Do not open the blister pack that contains the tablet until you are ready to take it. Remove the tablet from the blister pack by peeling back the foil, then taking the tablet out. Do not push the tablet through the foil. Place the tablet in your mouth. It should melt quickly. After the tablet has melted, swallow or take a drink of water.

If a Dose is Missed:
If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, wait until then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Keep the disintegrating tablet in the original package until you are ready to take it.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any outdated medicine or medicine no longer needed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
You must be careful if you are also using other medicine that might cause similar side effects as olanzapine. This includes medicine that might cause low blood pressure, overheating, or liver problems.
Make sure your doctor knows about all other medicines you are using.
Make sure your doctor knows if you are also using carbamazepine (Tegretol®), fluoxetine (Prozac®), fluvoxamine (Luvox®), levodopa (Sinemet®, Stalevo®), omeprazole (Prilosec®), or rifampin (Rifadin®).
Make sure your doctor knows if you are also using medicine to treat high blood pressure. Some blood pressure medicines are atenolol, hydrochlorothiazide (HCTZ), lisinopril, metoprolol, quinapril, Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, and Zestril®.
Make sure your doctor knows if you are using medicine to treat anxiety such as alprazolam, diazepam, Valium®, or Xanax®. Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Tell your doctor if you smoke. You might need a different amount of this medicine if you smoke.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or breast feeding, or if you have diabetes, liver disease, prostate problems, or glaucoma. Tell your doctor if you have a history of seizures, breast cancer, or severe constipation.

Make sure your doctor knows about any heart or blood problems you have now or have had in the past. This includes heart rhythm problems or a stroke.

Tell your doctor if you have ever had neuroleptic malignant syndrome (NMS) caused by any medicine for psychiatric disorders.

This medicine may raise or lower your blood sugar, or it may cover up symptoms of very low blood sugar (hypoglycemia).

Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep all appointments.

This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert. Sit or lie down until you no longer feel dizzy. Get up slowly.

This medicine might reduce how much you sweat. Your body could get too hot if you do not sweat enough. If your body gets too hot, you might feel dizzy, weak, tired, or confused. You might vomit or have an upset stomach. Do not get too hot while you are exercising. Avoid places that are very hot. Call your doctor if you are too hot and cannot cool down.

Some side effects are more likely to happen in elderly people who have memory problems or other reduced mental skills. Make sure the doctor knows if the person who will be using this medicine has Alzheimer's disease or similar problems (often called "**dementia**").

Zyprexa® Zydis® contains phenylalanine (aspartame). This is only a concern if you have a disorder called phenylketonuria (a problem with amino acids). If you have this condition, talk to your doctor before using this medicine.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.

Change in how much or how often you urinate.

Fast or uneven heartbeat.

Fever, sweating, confusion, muscle stiffness.

Increased restlessness or excessive movements.

Jerky muscle movement you cannot control (often in your face, tongue, or jaw).

Numbness or weakness in your arm or leg, or on one side of your body.

Severe sleepiness, slurred speech, trouble breathing.

Trouble swallowing.

If you notice these less serious side effects, talk with your doctor:

Constipation, upset stomach.

Dry mouth, increased thirst.

Light-headedness or fainting.

Missed menstrual period.

Redness or swelling in your eye.

Shakiness, problems with balance or walking.

Swelling in your hands, ankles, or feet.

Swollen breasts, or liquid discharge from your nipples (men or women).

Weakness.

Weight gain.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

**B)** OLANZAPINE (Injection)
Olanzapine

Treats an episode of agitation (being overexcited, tense, hostile, or anxious) in a person who has schizophrenia or bipolar I disorder.

When This Medicine Should Not Be Used:
You should not use this medication if you have ever had an allergic reaction to olanzapine.

How to Use This Medicine:
Injectable
A nurse or other trained health professional will give you this medicine.
Your doctor will prescribe your exact dose and tell you how often it should be given. This medicine is given as a shot into one of your muscles.
If your doctor wants you to keep using this medicine, you will need to change to the oral (tablet) form.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
You must be careful if you are also using other medicine that might cause similar side effects as olanzapine. This includes medicine that might cause low blood pressure, overheating, or liver problems.
Make sure your doctor knows about all other medicines you are using.
Make sure your doctor knows if you are also using carbamazepine (Tegretol®), fluoxetine (Prozac®), fluvoxamine (Luvox®), levodopa (Sinemet®, Stalevo®), omeprazole (Prilosec®), or rifampin (Rifadin®).
Make sure your doctor knows if you are also using medicine to treat high blood pressure. Some blood pressure medicines are atenolol, hydrochlorothiazide (HCTZ), lisinopril, metoprolol, quinapril, Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, and Zestril®.
Make sure your doctor knows if you are using medicine to treat anxiety such as alprazolam, diazepam, Valium®, or Xanax®. Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.
Tell your doctor if you smoke. You might need a different amount of this medicine if you smoke.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breast feeding, or if you have diabetes, liver disease, prostate problems, or glaucoma. Tell your doctor if you have a history of seizures, breast cancer, or severe constipation.
Make sure your doctor knows about any heart or blood problems you have now or have had in the past. This includes heart rhythm problems or a stroke.
Tell your doctor if you have ever had neuroleptic malignant syndrome (NMS) caused by any medicine for psychiatric disorders.
This medicine may raise or lower your blood sugar, or it may cover up symptoms of very low blood sugar (hypoglycemia).
Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep all appointments.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert. Sit or lie down until you no longer feel dizzy. Get up slowly.
This medicine might reduce how much you sweat. Your body could get too hot if you do not sweat enough. If your body gets too hot, you might feel dizzy, weak, tired, or confused. You might vomit or have an upset stomach. Do not get too hot while you are exercising. Avoid places that are very hot. Call your doctor if you are too hot and cannot cool down.

Some side effects are more likely to happen in elderly people who have memory problems or other reduced mental skills. Make sure the doctor knows if the person who will be using this medicine has Alzheimer's disease or similar problems (often called "**dementia**").

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.
Change in how much or how often you urinate.
Fast or uneven heartbeat.
Fever, sweating, confusion, muscle stiffness.
Increased restlessness or excessive movements.
Jerky muscle movement you cannot control (often in your face, tongue, or jaw).
Numbness or weakness in your arm or leg, or on one side of your body.
Severe sleepiness, slurred speech, trouble breathing.
Trouble swallowing.

If you notice these less serious side effects, talk with your doctor:
Constipation, upset stomach.
Dry mouth, increased thirst.
Light-headedness or fainting.
Missed menstrual period.
Pain where the shot is given.
Redness or swelling in your eye.
Shakiness, problems with balance or walking.
Swelling in your hands, ankles, or feet.
Swollen breasts, or liquid discharge from your nipples (men or women).
Weakness.
Weight gain.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

**4.3 Place In Therapy**

**A)** Clinical effects of olanzapine appear similar to those of clozapine in schizophrenic patients. Olanzapine when compared to haloperidol has improved negative symptoms and is associated with a lower incidence of extrapyramidal effects. Olanzapine has been shown to be superior in overall efficacy to haloperidol and studies suggest the possibilities that maintenance of long-term response may be better than haloperidol (Beasley et al, 1997; Kando et al, 1997). Olanzapine is considerably more expensive than haloperidol, however, savings have been demonstrated that make the 2 agents approximately equivalent in cost (Almond & O'Donnell, 1998). These include olanzapine's reduced need for medical services due to lower relapse rates and its greater efficacy in alleviating symptoms.
**B)** Olanzapine offers a potential advantage over clozapine as it does not appear to cause severe neutropenia or agranulocytosis. Other possible advantages relative to clozapine are a lower propensity to induce orthostatic hypotension, tachycardia, seizures, and hyperthermia, although these are suggested simply by their absence in clinical trials. Clozapine is primarily indicated in severely disturbed patients who are refractory to typical antipsychotics, and in patients with intolerable extrapyramidal symptoms (including tardive dyskinesia) related to other agents. Olanzapine may have a similar role, although further studies are needed. Without the restrictions imposed by a risk of agranulocytosis, indications for olanzapine may be extended (eg, first-line therapy in some types of patients). More studies in various types of psychosis are needed (eg, schizoaffective disorders, psychotic mood disorders, major depression with psychotic features, psychosis in parkinsonian patients). Olanzapine is effective for treating schizophrenia and has a favorable adverse effect profile (Bever

& Perry, 1998).

**4.4 Mechanism of Action / Pharmacology**

**A)** MECHANISM OF ACTION

**1)** Olanzapine is an antipsychotic agent (thienobenzodiazepine derivative) structurally similar to clozapine. Pharmacologic effects of olanzapine are also similar to those of clozapine, and both agents are classified as "atypical" antipsychotic agents mainly by virtue of their efficacy in treating negative (and positive) symptoms of schizophrenia and lower propensity for extrapyramidal effects compared to conventional or typical antipsychotics (eg, haloperidol) (Moore et al, 1992; Anon, 1994). A disadvantage of clozapine is its ability to induce agranulocytosis in up to 2% of patients; olanzapine was primarily developed as equally effective but safer alternative (Anon, 1994; AMA Department of Drugs, 1994).

**2)** Similar to clozapine, olanzapine is both a dopamine (D) and serotonin (5-HT) antagonist; both compounds have greater in vivo potency for antagonizing 5-HT-mediated than D-mediated responses (Moore et al, 1992; Fuller & Snoddy, 1992). Receptor binding studies have shown that olanzapine has high affinity for D1, D2, D4, 5-HT2A, and 5-HT2C receptors, as well as histamine-1, alpha-1 adrenergic, and muscarinic (particularly M1) receptors (Anon, 1994; Beasley et al, 1996; Anon, 1994a; Higgins, 1993). The drug binds more potently to the 5-HT2A receptor than the D2 receptor (3-fold); greater activity at D4 compared to D2 receptors has also been reported (Tollefson et al, 1994; Fuller & Snoddy, 1992; Beasley et al, 1996). Results of neuroendocrine studies in animals suggest that olanzapine is more potent than clozapine with respect to blockade of 5-HT2 and D2 receptors (Fuller & Snoddy, 1992).

**3)** Olanzapine induces near saturation of the 5-HT(2) receptor at all doses (Kapur et al, 1998). Even a dose of 5 mg/day induces saturation of greater than 90%. D(2) occupancy, however, is dose-related:

DOSE
D(2) RECEPTOR OCCUPANCY
5 mg/day
55%
10 mg/day
73%
15 mg/day
75%
20 mg/day
76%
20 mg/day
83%

**4)** D(2) receptor occupancy was measured at 88% in a single patient taking olanzapine 40 mg/day.

**B)** REVIEW ARTICLES

**1)** A review of the side effects of antipsychotic medications, including olanzapine, in the elderly is available. Of particular importance in this population is the high incidence of sedation and abnormal gait which can lead to falls and other accidents (Masand, 2000).

**2)** Reviews of the adverse effects related to olanzapine are available. The management of these side effects, including sedation, tremor, dry mouth, increased appetite, and weight gain is discussed (Zarate, 2000). Safety data from comparative clinical trials is also available (Conley & Meltzer, 2000).

**3)** Comprehensive reviews on olanzapine have been published (Tollefson & Kuntz, 1999; Falsetti, 1999; Bever & Perry, 1998a; Kando et al, 1997a).

**4)** The pharmacologic properties and therapeutic efficacy of olanzapine in the management of psychoses are reviewed (Fulton & Goa, 1997).

**5)** An indepth overview of the efficacy of olanzapine in clinical trials has been published (Beasley et al, 1997).

**6)** A review of clinical trails evaluating olanzapine dosing is available (Nemeroff, 1997).

**7)** A study reviewing the safety profile of olanzapine has been published (Beasley et al, 1997a).

**8)** The use of atypical antipsychotic medications in adults (Markowitz et al, 1999; Brown et al, 1999), older adults (Chan et al, 1999), and children (Malone et al, 1999; Lewis, 1998; Toren et al, 1998) has been

reviewed.
**9)** The mechanisms of neuroleptic-induced extrapyramidal symptoms and tardive dyskinesia and their relationship to atypical antipsychotic agents was reviewed (Glazer, 2000).
**10)** A review of atypical antipsychotics in the treatment of drug-induced psychosis in Parkinson's disease was completed (Friedman & Factor, 2000).

**4.5 Therapeutic Uses**

**4.5.A Adverse reaction to cannabis - Induced psychotic disorder**

**1)** Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
**2)** Summary:
As effective as haloperidol
**3)** Adult:
**a)** Olanzapine was as effective as haloperidol in the treatment of cannabis-induced psychotic disorder (Berk et al, 1999). In a double-blind study, patients with a psychotic episode associated with cannabis use were randomized to receive either olanzapine 10 milligrams (n=15) or haloperidol 10 mg (n=15). After 4 weeks there was a significant improvement in both groups as compared to baseline measured on the Brief Psychiatric Rating Scale (p=0.0002 for olanzapine, p=0.0001 for haloperidol). There was no significant difference between the 2 groups. Olanzapine was associated with fewer extrapyramidal side effects.

**4.5.B Agitation - Manic bipolar I disorder - Schizophrenia**

FDA Labeled Indication
**1)** Overview
FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
**2)** Summary:
Intramuscular olanzapine is indicated for the treatment of AGITATION ASSOCIATED WITH SCHIZOPHRENIA OR BIPOLAR I MANIA
Oral olanzapine has been used for the treatment of acute agitation in patients with schizophrenia or bipolar disorder
**3)** Adult:
**a)** Intramuscular olanzapine effectively reduced symptoms of agitation in patients with schizophrenia or bipolar disorder in 3 short-term, placebo-controlled trials. The primary efficacy measure in these trials was the change in the Positive and Negative Syndrome Scale (PANSS) Excited Component from baseline to 2 hours post-injection. The mean baseline PANSS Excited Component score was 18.4 (range, 13 to 32) out of a maximum score of 35, suggesting mostly moderate levels of agitation. The first trial included agitated inpatients meeting DSM-IV criteria for schizophrenia (n=270). Four fixed intramuscular olanzapine doses (2.5 mg, 5 mg, 7.5 mg and 10 mg) were evaluated and all doses were significantly better as compared with placebo on the PANSS Excited Component at 2 hours post-injection. However, the effect was larger and more consistent for the 5 mg, 7.5 mg, and 10 mg doses.
In a second placebo-controlled trial, agitated inpatients with schizophrenia (n=311), received a fixed 10

mg dose of intramuscular olanzapine or placebo. Again, olanzapine was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection. In the third trial, agitated inpatients with Bipolar I Disorder (and acute manic or mixed episode with or without psychotic features) (n=201), received one fixed intramuscular olanzapine dose of 10 mg or placebo. Olanzapine was significantly better as compared with placebo on the primary outcome measure. Examination of population subsets such as age, race, and gender did not show any differential responsiveness on the basis of these sub-groupings (Prod Info Zyprexa(R) IntraMuscular, 2004).

**b)** Rapid initial dose escalation (RIDE) of olanzapine was effective in the treatment of acute agitation in patients with schizophrenia or bipolar disorder. In a randomized, double-blind, multicenter study, acutely agitated patients (n=148) received either RIDE therapy (olanzapine 20 to 40 milligrams (mg)/day for 2 days, then 20 to 30 mg/day for 2 days) or "usual clinical practice" (UCP) therapy (olanzapine 10 mg/day plus lorazepam as needed) for 4 days of blinded treatment before entering an open-label phase in which all patients received olanzapine 5 to 20 mg/day for 3 days. Both the RIDE and UCP therapies produced significant mean reductions in the Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) score from baseline to 24 hours (mean reduction, -7.01 and -5.51, respectively, p less than 0.001, both values). However, patients in the RIDE group showed greater improvements in agitation those in the UCP group on days 2, 3, and 4 as measured by mean changes in PANSS-EC scores (p=0.03, p=0.08, p=0.001, respectively). Adverse events were similar in both groups with headache, somnolence, dizziness, nervousness, and insomnia being reported most frequently reported (Baker et al, 2003).

**4.5.C Alzheimer's disease - Psychotic disorder**

**1)** Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**2)** Summary:

Olanzapine doses of 5 or 10 mg daily were safe and effective in decreasing behavioral and psychotic symptoms associated with Alzheimer's disease in elderly patients
Somnolence and gait disturbances increased in olanzapine-treated patients

**3)** Adult:

**a)** Low doses of olanzapine (5 milligrams (mg) or 10 mg daily (QD)) were safe and significantly superior to placebo in the treatment of behavioral and psychotic symptoms associated with Alzheimer's disease in elderly patients. In a 6-week, multicenter, double-blind, placebo-controlled trial, 206 nursing home residents were randomized to receive a fixed daily dose of olanzapine 5, 10, or 15 mg or placebo. Efficacy was measured using the sum of scores for agitation, aggression, hallucinations, and delusion items ("Core Total") of the Neuropsychiatric Inventory-Nursing Home scoring system and the Occupational Disruptiveness score, to assess patient-related caregiver distress. Core Totals were significantly improved in patients receiving 5 mg and 10 mg doses, while Occupational Disruptiveness scores were significantly reduced in those receiving 5 mg doses. Somnolence occurred significantly more often in patients receiving olanzapine than placebo. Gait disturbances were more common in those receiving olanzapine 5 or 15 mg daily. Frequencies of significant cognitive impairment, increased extrapyramidal symptoms, and central anticholinergic effects in olanzapine-treated patients were similar to those of placebo-treated patients (Street et al, 2000). In an 18-month, open extension of this trial with 105 patients, behavioral and psychotic symptoms continued to decrease, with the final average Core Total score having decreased to 6 from 7.9 at the start of the open trial (p=0.002). Nearly half of the patients showed a 50% or greater additional reduction in Core Total score. Measures of cognitive status showed no change. Levels of akathisia continued to improve (p=0.018); extrapyramidal symptoms and parkinsonian symptoms did not increase. Although weight did not change significantly for the group overall, some individuals had significant weight gain (average, 4.3 kilograms) or weight loss (average, 4.4 kilograms). Somnolence and accidental injury continued to be the most common adverse events. Five

milligrams was the modal dose (the dose prescribed for a patient for the most number of days) for two-thirds of the patients during the open trial (Street et al, 2001).

**4.5.D Anorexia nervosa**

**1)** Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**2)** Summary:
Effective treatment in small, open-label trial in patients with anorexia nervosa
Effective in 1 case report of anorexia nervosa with obsessive-compulsive symptoms
See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

**3)** Adult:

**a)** Weight gain occurred in patients with anorexia nervosa when treated with olanzapine. In a small, open-label trial, patients with anorexia nervosa (restricting or binge/purge subtype) without schizophrenia, schizoaffective disorder or bipolar disorder received olanzapine 10 milligrams (mg) once daily for 10 weeks (n=18). Patients attended weekly group psychoeducational sessions. Of the 14 patients that completed the study, 10 patients had a mean weight gain of 8.75 pounds and 4 patients lost an average of 2.25 pounds. Of these patients, those that gained weight had significantly different mean weights at day 1 as compared to both week 5 and week 10 (p=0.0195 and p=0.0092, respectively). Three patients attained their ideal body weight. The most common adverse event was sedation. Controlled studies are needed to substantiate these findings (Powers et al, 2002).

**b)** Body weight, appetite, and self-image were restored with olanzapine 5 milligrams (mg) daily in 3 women. Patients with a 12 year or more history of anorexia nervosa gained 9 to 19 kilograms over several months. At the time of publication, patients continued to receive olanzapine 5 mg daily. Because it takes a few weeks before a full antipsychotic effect is achieved, patients should be encouraged to continue with olanzapine therapy within the first 2 months (Jensen & Mejlhede, 2000).

**c)** A 49-year-old woman with anorexia nervosa and obsessive- compulsive symptoms improved with olanzapine therapy (Hansen, 1999). The woman's obsessive-compulsive problems were mainly fear of food contamination, preoccupation with nutritional issues, confusion, and seriously disturbed body image. She had no insight into her problems and was depressed. She weighed 31.2 kilograms when she was started on olanzapine 5 milligrams daily. Over the following months, her confusion cleared and her insight changed markedly. Approximately 6 months later her weight had increased to 53.1 kg.

**4.5.E Anxiety - Dementia**

**1)** Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**2)** Summary:
Reduced anxiety in elderly **dementia** patients

**3)** Adult:

**a)** Olanzapine treatment reduced anxiety in elderly patients with Alzheimer's-type **dementia** independently of improvement in hallucinations, treatment-caused somnolence, or benzodiazepine use. A post hoc analysis was performed on a subset of patients (n=120) from a larger, randomized, double-blind trial that evaluated the efficacy of olanzapine (3 dosages) versus placebo for 6 weeks for the treatment of psychosis and agitation/aggression due to Alzheimer's disease. The subgroup (mean age 83 years) was

selected for exhibiting clinically significant anxiety, defined as a score of 2 or higher on the anxiety item of the Neuropsychiatric Inventory/Nursing Home instrument (NPI/NH). Anxiety scores of patients receiving olanzapine 5 milligrams (mg) per day improved significantly more than scores of patients receiving placebo (p=0.034). Improvement in anxiety with olanzapine 5 mg/day remained statistically superior even after controlling for improvement in hallucinations. With higher doses of olanzapine (10 and 15 mg/day), improvement in anxiety scores was not significantly different from that with placebo. Somnolence was the only adverse effect that occurred significantly more frequently with olanzapine than with placebo. None of the individual peripheral or central potential anticholinergic adverse events occurred more frequently with olanzapine than with placebo. However, peripheral anticholinergic effects collectively occurred more frequently with olanzapine 15 mg/day than with placebo (26% vs 6%, p=0.008). There was no difference between olanzapine and placebo treatments in the occurrence of extrapyramidal symptoms (Mintzer et al, 2001).

**4.5.F Bipolar disorder, Maintenance**

FDA Labeled Indication

**1)** Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**2)** Summary:

Indicated for maintenance monotherapy in bipolar patients who have responded to initial treatment with olanzapine

**3)** Adult:

**a)** Continuation olanzapine therapy was more effective than placebo in delaying the time to relapse in patients with bipolar disorder. In a randomized, double- blind, placebo-controlled trial, bipolar patients with a mixed or manic episode who responded to initial, open-label olanzapine therapy (5 to 20 milligrams (mg)/day for approximately two weeks) received either continuation of olanzapine at their same dose (n=225) or placebo (n=136) for observation of relapse. Response during the initial phase of the study was defined as a decrease in the Young Mania Rating Scale (Y-MRS) total score to 12 or less and a decrease in the Hamilton Depression Rating Scale (HAM-D) score to 8 or less. Relapse was defined as an increase of the Y-MRS or HAM-D total score to 15 or greater, or hospitalization for either mania or depression. Patients treated with olanzapine showed a significantly longer time to relapse as compared with patients given placebo (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).

**4.5.G Bipolar disorder, manic episode**

FDA Labeled Indication

**1)** Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**2)** Summary:

Indicated for the treatment of acute manic or mixed episodes associated with bipolar I disorder
The combination of olanzapine with lithium or valproate is indicated for the short-term treatment of acute manic episodes associated with bipolar I disorder

**3)** Adult:

**a)** MONOTHERAPY

**1)** In a small open-label study, olanzapine was found to be somewhat effective as an adjunctive treatment of patients with bipolar disorder (BPD) Twenty-three, severely ill, BPD patients (10 men) with a history of poor response or intolerance to therapeutic concentrations of lithium, valproate or carbamazepine were enrolled in this long-term study (mean 303 days). The Clinical Global Impressions Scale for use in bipolar illness (CGI-BP) was used to assess olanzapine effectiveness. The depression subscale decreased by 0.9 (p less than 0.006), the mania subscale by 1.6 (p less than 0.001), and the general score decreased by 1.3 (p less than 0.0003). Ten of the 23 patients had a decrease of at least 2 points on the CGI-BP at endpoint, but only 2 patients were rated as in remission. There were 6 dropouts in the study, 2 due to adverse effects, 2 due to lack of response, 1 because of overdose, and one lost to follow-up. The mean final dose of olanzapine was 8.2 milligrams (mg) per day with 16 patients taking lithium, 8 taking carbamazepine, 3 receiving valproate and one each taking gabapentin and lamotrigine concurrently. The most common adverse events were somnolence (17%) and weight gain (13%). No new cases of tardive dyskinesia were reported during the study (Vieta et al, 2001).

**2)** Olanzapine was more effective than placebo in the treatment of patients with acute bipolar mania. In a randomized, double-blind, parallel study, 115 patients were assigned to receive olanzapine 5 to 20 milligrams (mg) daily (QD) (n=55) or placebo (n=60) for 4 weeks. Olanzapine-treated patients demonstrated significantly greater mean improvement in symptoms over placebo, as determined by the total Young-Mania Rating Scale (YMRS). Improvement was clinically evident within the first week of treatment and was maintained throughout the study. Significantly more olanzapine-treated patients demonstrated a 50% or more decrease in total YMRS score from baseline (65% versus 43%, p=0.02) and euthymia as measured by a total YMRS score of 12 or higher at endpoint) (61% versus 36%, p=0.01). The incidence of extrapyramidal symptoms was similar between olanzapine- and placebo-treated patients. However, weight gain, treatment-emergent somnolence, and elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) occurred significantly more often in olanzapine-treated patients (Tohen et al, 2000).

**3)** Olanzapine exhibited superior efficacy over placebo in the treatment of acute mania (Tohen et al, 1999; Prod Info Zyprexa(R), 2000a). In a double-blind study, patients with manic or mixed episodes associated with bipolar disorder were randomized to receive either olanzapine 10 milligrams (mg) (n=70) or placebo (n=69). The olanzapine dose could be adjusted between a range of 5 to 20 mg daily. At the end of 3 weeks the mean modal dose of olanzapine was 14.9 mg daily. The olanzapine group had a significantly greater improvement in total scores on the Young Mania Rating Scale at week 3 (p less than 0.02). Olanzapine was well-tolerated with no drop-outs due to adverse effects.

**4)** In 2 case reports, olanzapine effectively augmented mood stabilizers in 2 patients with nonpsychotic bipolar mixed mood states (Ketter et al, 1998). The first was a 34-year-old male with bipolar I disorder that entered a nonpsychotic mixed mood state after increased occupational and familial stress. He had previously been euthymic on lithium and divalproex. Olanzapine 10 milligrams (mg) was added at bedtime and, with the initial dose, the patient slept well for the first time in over 2 weeks. He reported complete remission of his symptoms by the next morning. A 47-year-old woman with bipolar I disorder escalated to a mixed mood state after previously taking divalproex, lorazepam, and levothyroxine. Olanzapine 10 mg was added at bedtime and she slept well for the first time in 10 days. Her mood was also improved by the next morning. Both of these patients had rapid improvements which the authors admit may have been an indirect benefit of improved sleep with olanzapine or may have actually been due to a direct mood stabilization effect.

**b)** COMBINATION THERAPY

**1)** In patients with bipolar manic or mixed episodes who do not respond adequately to lithium or valproate, addition of olanzapine increases efficacy of treatment. In a randomized, double-blind, placebo-controlled trial, patients with bipolar disorder who had responded inadequately to 2 or more weeks of therapy (ie, maintaining a score of 16 or more on the Young Mania Rating Scale (YMRS)) received either olanzapine (flexible dose range of 5, 10, 15 or 20 milligrams/day)(n=229) or placebo (n=115). Both groups improved during the course of treatment, but the olanzapine group showed a 59% improvement in YMRS score from baseline, while the monotherapy group improved by 40% (p=0.003). Particular items of the YMRS that improved more with cotherapy were irritability, speech, language/thought disorder, and disruptive/aggressive behavior. Sixty-eight percent of the

cotherapy group were responders (50% or greater improvement in YMRS score), compared to 45% of the montherapy group (p=0.01). Median time to response was 18 days with cotherapy and 28 days with monotherapy. Patients in the cotherapy group showed significantly greater improvement in depression scores than did those in the monotherapy group (p less than 0.001). Among patients experiencing a mixed episode with moderate to severe depression, the mean decrease in the Hamilton Depressive scale from baseline to 6 weeks was 10.3 for cotherapy and 1.6 for monotherapy (p less than 0.001). The most frequently reported adverse events in the cotherapy group were somnolence, dry mouth, weight gain, increased appetite, tremor, and speech disorder. No statistically significant changes from baseline were observed in extrapyramidal symptoms (Tohen et al, 2002a).

**2)** Combination therapy with olanzapine and lithium or valproate was effective in the treatment of acute manic episodes in patients with bipolar disorder with manic or mixed episodes. In two 6-week, randomized, placebo-controlled trials, patients (n=175, n=169) on lithium or valproate therapy with uncontrolled manic or mixed symptoms and with a score of 16 or higher on the Young Mania Rating scale (Y-MRS) received either olanzapine (dose range of 5 to 20 milligrams (mg) once daily, starting at 10 mg/day) or placebo, in combination with their original lithium (in a therapeutic range of 0.6 milliequivalents/liter (mEq/L) to 1.2 mEq/L) or valproate (in a therapeutic range of 50 micrograms/milliliter (mcg/mL) to 125 mcg/mL) therapy. In both trials, olanzapine in combination with lithium or valproate was more effective than either lithium or valproate alone in reducing the total Y-MRS score (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).

**4)** Pediatric:

**a)** MONOTHERAPY

**1)** Olanzapine monotherapy effectively treated symptoms of psychosis, depression, and mania in a group of 23 youths diagnosed with pediatric bipolar disorder (BPD). In this open-label, 8-week study, 23 youths, 5 to 14 years old, discontinued their current BPD treatments and were started on olanzapine 2.5 milligrams (mg) per day. Olanzapine was increased by 2.5 mg/day every 3 days to a maximum dose of 20 mg/day (mean dose at endpoint was 9.6 +/- 4.3 mg per day). Lorazepam (up to 4 mg/day) and benztropine (up to 2 mg/day) were allowed as needed for rescue medication and for extrapyramidal symptoms respectively. Patients taking guanfacine or clonidine for attention deficit hyperactivity disorder (ADHD) were allowed to continue their medications, but could not adjust the dose during the study. Psychiatric symptoms were assessed at baseline and once weekly using the Young Mania Rating Scale (YMRS), the Clinical Global Impressions Severity Scale (CGI-S), the Brief Psychiatric Rating Scale (BPRS), and the Children's Depression Rating Scale (CDRS). Extrapyramidal symptoms were assessed on the same schedule using the Simpson-Argus Scale, the Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale (AIMS). Significant improvement from baseline to endpoint was noted on YMRS (62%, p less than 0.001), CGI-S (38%, p less than 0.001), and BPRS (62%, p less than 0.001). The most frequently reported adverse effects were increased appetite (n=14), somnolence (n=10), abdominal pain (n=7) and weight gain (n=7). There was no significant difference in extrapyramidal symptoms during the study, although 2 patients had treatment-emergent akathisia. There were small statistically significant decreases in hematocrit, hemoglobin, and mean cell volume and statistically significant increases in alanine transferase (ALT) and prolactin levels. One patient dropped out of the study after 6 weeks due to worsening of depressive symptoms (Frazier et al, 2001).

### 4.5.H Borderline personality disorder

**1)** Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**2)** Summary:

Improved symptoms in all 4 cores areas of BPD in a 6-month study

**3)** Adult:

**a)** Olanzapine was superior to placebo for reducing symptoms of borderline personality disorder (BPD) in a small study. Thirty women who met DSM-IV criteria for BPD and did not meet criteria for major depression were randomized in a 2:1 ratio to receive olanzapine or placebo in a double-blind manner for 6 months. The starting dose of olanzapine was 1.25 milligrams/day and was adjusted according to perceived response and side effects. The mean daily dose at endpoint was 5.3 mg. Olanzapine was significantly more effective than placebo in the affective area of anxiety (p=0.002) but not in depression (p=0.357), in the cognitive area of paranoia (p=0.003), and in the area of trouble relationships (p=0.016). Subjects in the olanzapine group had significantly greater weight gain than did subjects in the placebo group (p=0.012). However, average weight gain of olanzapine- treated subjects was small: 2.9 pounds. No tardive dyskinesia or other movement disorders were observed (Zanarini & Frankenburg, 2001).

**4.5.I Cancer - Nausea**

**1)** Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**2)** Summary:

Preliminary data indicated safety and efficacy in patients with moderate nausea related to advanced cancer and associated pain

**3)** Adult:

**a)** In an open-label, pilot study of 15 patients with advanced cancer and associated pain, the administration of olanzapine produced a significant reduction in nausea. Patients aged 20 to 80 years with primarily breast, lung, and ovarian cancers and moderate nausea received olanzapine 2.5 milligrams (mg), 5 mg, and 10 mg sequentially for 2 days after a 2-day washout and placebo run-in period. Nausea was measured using the nausea item on the Functional Assessment of Cancer Treatment- General (FACT-G) scale. Overall quality of life, also measured by FACT-G scores, was highest at the 5 mg dose level. As measured by the Barnes Akathisia Scale, the Simpson Angus Scale, the Mini Mental Status Exam, adverse effects related to olanzapine were minimal and similar and not different between doses administered (Passik et al, 2002).

**4.5.J Catatonia**

**1)** Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**2)** Summary:

Olanzapine was effective in the treatment of catatonia in one case report

**3)** Adult:

**a)** A 16-year-old African American male was successfully treated for catatonia with a combination of lorazepam, valproic acid, and olanzapine. Prior to admission, the patient had become increasingly noncommunicative and had not slept for 1 week. He was unable to follow simple commands, eat, and was incontinent of urine and feces. An electroencephalogram (EEG) showed diffuse mild slowing without any evidence of seizure activity. Lorazepam was initiated at a dose of 1 milligram (mg) four times daily (QID) and increased to 2 mg three times daily (TID) without improvement in symptoms. On day 4, valproic acid was started, and 3 days later, olanzapine was added and titrated to 10 mg twice daily

(BID). Over the next 14 days, the patient began to play video games, socialize and attempted to wash and dress himself. On day 21, lorazepam was tapered and discontinued due to excessive sedation after the addition of olanzapine. Valproic acid was discontinued on day 28 By day 42, the patient was interacting with peers and communicating in full sentences. Eight weeks after admission, the patient was discharged, experiencing only an occasional auditory hallucination. Olanzapine therapy was continued and catatonia has not recurred after 1 year (DelBello et al, 2000).

**4.5.K Cocaine dependence**

**1)** Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
**2)** Summary:
Olanzapine was ineffective in the treatment of cocaine dependence
**3)** Adult:
**a)** Olanzapine was not an effective therapy for the treatment of cocaine dependence. In a randomized, placebo-controlled, double-blind pilot trial, cocaine dependent patients (n=30) received olanzapine (initial, 2.5 milligrams (mg)/day, titrated to 10 mg/day) or placebo for 11 weeks following a 1-week baseline phase. Urine benzoylecgonine tests (UBT) were obtained twice a week. A significant time by medication group interaction was observed with regard to the UBT results whereby the estimated odds of a positive UBT went up by 4% between visits for olanzapine-treated patients (95% CI=0.975 to 1.068), and was reduced by 6% for patients in the placebo group (95% CI=0.920 to 0.968) (p=0.01). In addition, treatment retention was better in the placebo group as compared with the olanzapine group. Patients in the placebo group attended a significantly greater median number of treatment sessions than patients in the olanzapine group (22 vs 18, respectively; p=0.029). Finally, olanzapine was not superior to placebo in any of the secondary outcome measures including cocaine craving, mood and anxiety symptoms, and self-reported cocaine use. The most common adverse effects reported during the study included weight gain (40%), drowsiness (40%), constipation (13%), dizziness (10%), dry mouth (7%), nausea (7%), restlessness (7%), and urticaria (3%) (Kampman et al, 2003).

**4.5.L Delirium**

**1)** Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
**2)** Summary:
May produce significant improvement in patients with delirium
Attenuated delirium in hospitalized cancer patients, with no report of any extrapyramidal effects
**3)** Adult:
**a)** A 7-day course of oral OLANZAPINE produced resolution of delirium or reduction of symptom severity in hospitalized cancer patients diagnosed with delirium (DSM-IV), according to an open-label observational study (n=79). Enrollees (mean age 60.6 years) had a mean Karnofsky score of 37, with delirium ranging from mild (17%) to moderate (61%) to severe (23%). Mean OLANZAPINE starting dose was 3 milligrams (mg), with titration to mean 4.6 mg at days 2 to 3 and mean 6.3 mg at days 4 to 7. Subjects were given olanzapine as a single dose at bedtime or in 2 divided doses in the morning and at bedtime. Overall, 57 patients (76%) achieved complete resolution of delirium (defined as a Memorial Delirium Assessment Scale (MDAS) score of 10 or lower). Scores on the MDAS decreased from

baseline 19.85 to 12.73 at day 2/3 (p=0.001) and to 10.78 at study end-point (days 4 to 7) (p=0.001). Based on regression analysis, factors most strongly associated with a poor response were age above 70 years, central nervous system spread of cancer, and hypoactive as the type of delirium. Other factors which tended to correlate with less successful outcomes were a history of **dementia**, severe delirium at baseline, and hypoxic delirium as the etiology. Side effects were few and relatively mild; sedation was the most commonly reported adverse effect (30% incidence). No extrapyramidal effects occurred in the cohort. Olanzapine was withdrawn in 2 subjects whose delirium seemed to worsen when taking the drug (Breitbart et al, 2002).

**b)** Fourteen patients given olanzapine demonstrated a 50% or greater reduction in delirium scores in an open-label study of 20 adult, Korean, patients (5 females), patients (mean age 46 years) with varying etiologies of delirium. Mean olanzapine treatment doses were 5.9 milligrams (mg) with maximal response occurring in an average of 3.8 days. The pretreatment Delirium Rating Scale (DRS) score showed a significant (p less than 0.01) decline from 20 to 9.3 following a mean duration of 6.6 days. Eleven of the 14 patients that had a 50% or greater decrease in DRS were leukemia patients; one patient with traumatic brain injury had a DRS score that increased from 19 to 21. None of the patients had comorbid psychiatric diagnoses or were taking other psychoactive medications during this study. The authors said that adverse effects due to olanzapine were minimal although there was no specific rating scale used or a placebo control group for comparison (Kim et al, 2001).

**c)** In an open-label study of 22 adult patients (mean age approximately 64 years) with varying etiologies of delirium, five of 11 patients given olanzapine and six of 11 patients given haloperidol showed marked improvement in the Delirium Rating Scale (DRS; greater than 50% decrease in score). Mean treatment doses were 8.2 milligrams (mg) with olanzapine and 5.1 mg with haloperidol. Pretreatment DRS were similar in both groups; 18 in the olanzapine and 20 in the haloperidol group. Mean improvement in the DRS was 7.6 with olanzapine and 10 with haloperidol. Peak response was seen at approximately 1 week with both agents. Some of the patients in each group had comorbid psychiatric diagnoses and were taking other psychoactive medications. None of the patients given olanzapine experienced side effects, while 3 haloperidol patients experienced extrapyramidal symptoms and 2 experienced excessive sedation (Sipahimalani & Masand, 1998).

**d)** A 59-year-old cancer patient with delirium was successfully treated with olanzapine (Passik & Cooper, 1999). Low-dose haloperidol failed to treat the patient's symptoms and she was started on olanzapine 5 milligrams (mg) daily. She improved dramatically within the first 24 hours and was increased to olanzapine 10 mg with 2.5 mg as needed during the day. Her mental status returned to normal over 72 hours.

### 4.5.M Dementia

See Drug Consult reference: BEHAVIORAL PROBLEMS - DEMENTIA-RELATED

### 4.5.N Depressed bipolar I disorder

**1)** Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**2)** Summary:

Olanzapine monotherapy and olanzapine plus fluoxetine combination therapy reduced depressive symptoms in patients with bipolar depression

**3)** Adult:

**a)** Both olanzapine monotherapy and olanzapine plus fluoxetine combination therapy were more effective than placebo in the treatment of bipolar depression. In a randomized, double-blind, placebo-controlled, multi- center, international study, patients with bipolar I disorder, depressed and a score of at

least 20 on the Montgomery-Asberg Depression Rating Scale (MADRS) received olanzapine (n=370; 5 to 20 milligrams (mg)/day; mean modal dose, 9.7 mg/day), olanzapine plus fluoxetine (n=86; 6 and 25 mg/day, 6 and 50 mg/day, or 12 and 50 mg/day; mean dose, 7.4 and 39.3 mg/day) or placebo (n=377) for 8 weeks. The primary objective of the study compared olanzapine monotherapy versus placebo with regard to change in the MADRS total score from baseline to 8 weeks. Throughout all 8 weeks of the study, treatments with both olanzapine and olanzapine-fluoxetine combination produced significantly greater reductions in depressive symptoms (as measured by the MADRS) as compared with placebo (p less than 0.001, all values). Also, a significantly greater improvement in the mean MADRS score at weeks 4, 6, and 8 were observed with olanzapine-fluoxetine combination therapy as compared with olanzapine monotherapy (p=0.01, p=0.02, p=0.01, respectively). The rate of response (defined as at least a 50% improvement in the MADRS total score and completion of at least 4 weeks of study) was significantly higher in olanzapine-treated patients as compared with placebo (39% vs 30.4%, respectively; p=0.02). Additionally, the response rate was significantly higher in the olanzapine-fluoxetine group as compared with both the placebo (56.1% vs 30.4%, respectively; p less than 0.001) and olanzapine groups (56.1% vs 39%, respectively; p=0.006). There were no statistically significant differences between groups with regard to rates of treatment-emergent mania. Adverse events were similar between the combination therapy and monotherapy groups, however, the olanzapine-fluoxetine group had a significantly higher rate of nausea and diarrhea (Tohen et al, 2003).

**4.5.O Depression, Treatment-resistant**

**1)** Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**2)** Summary:
Ineffective as a single agent in resistant depression
Possibly effective as augmentation therapy with antidepressants

**3)** Adult:

**a)** Some patients experiencing a recurrence of depression while under medical treatment responded very quickly to addition of olanzapine to their existing regimen. In a case series of 10 patients, 4 patients, all of whom had unipolar depression, were judged to be non-responders after 1 week of olanzapine treatment. Of the 6 responders, 5 had bipolar conditions and were receiving venlafaxine, desipramine, anafranil and citalopram, with 2 also taking epilim and 1 taking lithium. Each received olanzapine augmentation of 2.5 milligrams (mg) or 5 mg each night. Daily rating scores kept by the patients improved by 52% in the first day, 73% by day 4, and 89% by day 6. Anxiety and insomnia scores, in particular, showed notable improvement in the first 24 hours. Depressed mood showed linear improvement over the week. Two patients emerged with what they described as a "high." Because of the bipolar nature of the illness of the majority, it is uncertain whether the improvement with olanzapine was through an effect on a switching mechanism, leading to mild mania (Parker, 2002).

**b)** Patients with treatment-resistant, nonpsychotic, unipolar depression treated with olanzapine combined with fluoxetine showed significantly greater improvement than either agent alone across a variety of measures. In an 8-week, double-blind study, 28 patients (mean age 42 years) were randomized into 3 treatment groups: olanzapine plus placebo, fluoxetine plus placebo or olanzapine plus fluoxetine. The mean modal dose of olanzapine was 12.5 milligrams (mg) and 13.5 mg for the monotherapy and combined therapy groups, respectively. The mean modal dose of fluoxetine was 52 mg QD for both the monotherapy and combination group. Patients receiving combination therapy experienced greater improvements over baseline in Montgomery-Asberg Depression Rating Scale scores than with either agent alone and in total Hamilton Depression scale scores than olanzapine treatment alone. The proportion of patients responding (at least 50% improvement in Montgomery-Asberg Depression Rating Scale score) in the combination therapy group was significantly greater those receiving olanzapine alone

(60% versus 0%). Both drugs were well tolerated alone or in combination. Adverse effects included somnolence, increased appetite, asthenia, weight gain, headache, dry mouth, and nervousness. Increased appetite and weight gain occurred significantly more often in patients treated with olanzapine (Shelton,et al, 2001).

**4.5.P Drug-induced psychosis - Methamphetamine adverse reaction**

**1)** Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
**2)** Summary:
Successfully treated both acute and residual Psychotic states associated methamphetamine abuse
**3)** Adult:
**a)** Olanzapine successfully treated both acute and residual psychotic states associated in a 50-year-old male with a history of drug and alcohol abuse and a persistent paranoid-hallucinatory state after using methamphetamine for l year. Prior treatment with perphenazine and diazepam was unsatisfactory and the patient resumed his methamphetamine use. A trial of olanzapine 5 milligrams (mg) daily (QD) reduced the patient's acute psychotic symptoms within 2 weeks, although some doses were missed and occasional use of methamphetamine was reported. The olanzapine dose was increased to 5 mg twice daily and psychotic symptoms were eliminated, as long as abstinence from methamphetamine was maintained. Three weeks later, the patient discontinued his olanzapine, resumed frequent methamphetamine use, and became severely psychotic. The resumption of olanzapine significantly improved his psychosis and at his 16-week visit, the patient reported no residual psychotic symptoms or methamphetamine cravings. Adverse effects associated with olanzapine included weight gain and mild daytime somnolence (Misra et al, 2000).

**4.5.Q Essential tremor**

**1)** Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
**2)** Summary:
May be effective in the treatment of essential tremor
**3)** Adult:
**a)** Results of an open-label study suggest that olanzapine may be effective in the treatment of essential tremor. In this small, prospective trial, patients (n=37) with essential tremor received divided, oral doses of olanzapine 5 to 20 milligrams daily. Six months following initiation of therapy, the median tremor score was significantly reduced from 3.3 (baseline) to 1.12 (scale, 1 to 4; p=0.0001). Mild, transient sedation was the most common adverse event. Larger, well-controlled studies are needed to further substantiate these findings (Yetimalar et al, 2003).

**4.5.R Gilles de la Tourette's syndrome**

**1)** Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**2)** Summary:
Effective in a small study of 14 patients

**3)** Adult:

**a)** Olanzapine was found to be a safe and effective alternative to other antipsychotics for the treatment of Tourette's disorder. In a 6-week study of 14 patients, olanzapine was initiated at 10 milligrams daily with a maximum dose of 20 milligrams daily. The mean dose at the end of the trial was 15 milligrams/day. The Yale Global Tic Severity Scale (YGTSS) and the Clinical Global Impression Severity Scale (CGI) scores significantly decreased at days 14 and 42 compared to day 0 (p less than 0.005). The definition of treatment success (60% reduction in YGTSS score) was achieved by 50% of the patients and no difference was observed between the groups. The only side-effect observed was mild sedation which resolved as treatment continued and 2 patients experienced weight gain. The data suggests that olanzapine is safe and effective for the treatment of Tourette's disorder but more double-blind, placebo controlled trials are needed (Stamenkovic et al, 2000).

**4.5.S Headache**

**1)** Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**2)** Summary:
Effectively treated patients with chronic refractory headache who had failed previous therapies

**3)** Adult:

**a)** The results of a retrospective review indicate that olanzapine was effective in the treatment of patients with chronic refractory headache. A retrospective, unblinded review of fifty patient charts was conducted to assess the effectiveness of olanzapine treatment in patients with refractory chronic daily headache who had failed at least 4 previous preventative medication trials. Olanzapine doses ranged from 2.5 to 35 milligrams (mg) daily, however most patients received 5 mg (n=19) or 10 mg (n=17) per day. The mean number of headache days was significantly reduced from 27.5 days prior to treatment as compared to 21.1 days following treatment (p less than 0.001). Average headache severity scores were also significantly lower after treatment as compared to before treatment (2.2 vs 8.7, respectively; p less than 0.001). The most common adverse events were weight gain and somnolence. Controlled studies are needed to verify these findings (Silberstein et al, 2002).

**4.5.T Hemichorea**

**1)** Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**2)** Summary:
Effective in 1 case of hemichorea

**3)** Adult:

**a)** A 71-year-old woman with uncontrolled hypertension experienced complete resolution of her hemichorea with olanzapine therapy (Safirstein et al, 1999). She experienced involuntary movements of her left arm and leg. It had been ongoing for 3 days and worsened at rest. On computed tomography

scan, no lacunes or lesions were seen in the region of the subthalamic nucleus. Clinical improvement occurred with olanzapine 2.5 milligrams (mg); complete resolution of symptoms occurred with olanzapine 5 mg. She was lost to follow-up thereafter.

**4.5.U Huntington's disease**

**1)** Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
**2)** Summary:
Lessens involuntary movements
Decreases agitation, aggression, and delusions
**3)** Adult:
**a)** High dose olanzapine (30 milligrams (mg) per day) greatly improved chorea in a 30-year-old woman with Huntington's disease (HD). The woman had had HD for 6 years and in 2 days had a severe worsening of her chorea. She could not eat or dress without help and did not respond to haloperidol. She had no cognitive dysfunction or psychiatric abnormality. Her major deficits were in fine motor tasks, oral functions, chorea, and gait. She was treated with olanzapine 20 mg the first day and 30 mg/day thereafter. The chorea nearly stopped in the next 2 days, and she was able to eat and walk without assistance. She also showed improvement in fine motor tasks and gait. Her mild parkinsonism was not improved. Four months later, her improved condition was maintained (Bonelli et al, 2002).
**b)** Olanzapine improved cognition and function as measured by the Abnormal Involuntary Movement Scale (AIM) and Mini-Mental State Examination (MMSE) in a 49-year man with **dementia** resulting from Huntington's disease. Prior to admission, treatment with haloperidol 10 milligrams per day (mg/d), diazepam 10 mg/d, and tiapride 200 mg/d had been unsuccessful. Olanzapine 5 mg/d decreased the patient's impulsivity and demanding behavior. Increasing the dose to 10 mg/d was associated with improvement in chorea movements and ability to perform activities of daily living. After 4 months of olanzapine treatment, AIM score dropped from 40 to 22, MMSE improved from 20 to 26. At 5 months, the cessation of irritability and aggressive behavior, as well as improvements in movement disorders, cognitive ability and functional ability suggested therapeutic benefit was related to olanzapine. The influence of olanzapine on the serotonergic or dopaminergic receptor is theorized as a reason for these effects (Bogelman et al, 2001).
**c)** Olanzapine was used in combination with valproate in a 39-year old man and 52-year old woman to treat agitation, aggression, and delusions associated with Huntington's disease of 8 and 13 years duration, respectively. In the year prior to hospitalization, the patients' uncontrollable movements had become so severe neither could walk or assist in their care. Prior haloperidol treatment had been unsuccessful. Initially both patients were treated with olanzapine 10 milligrams (mg) daily (QD) and valproate 125 mg twice daily. Subsequently, the olanzapine dose was reduced to 5 mg QD (plasma level not measured) and valproate was increased to 500 mg three times daily (plasma concentrations from 60-80 micrograms per milliliter). After 7 to 8 weeks, both patients were discharged to nursing homes, able to walk with assistance, cooperative with eating, bathing, and social activities. Psychotic behavior and choreoathetoid movements decreased (Grove et al, 2000).
**d)** A man in his early 50's had marked improvement of his movement disorder associated with Huntington's disease with olanzapine therapy (Dipple, 1999). He had previously been treated with sulpiride, which was ineffective, and risperidone, which caused hypotension. Olanzapine 5 milligrams was initiated and he had a marked improvement in his involuntary movements within 1 week. He experienced slowed thinking but adjusting the time of the medication to evening improved this. He maintained his improvement in involuntary movements over the next 6 months. The authors hypothesized that since there is a loss of D2 projection neurons associated with Huntington's disease, the D2 antagonist properties of olanzapine may be beneficial in the improvement of the chorea.

**4.5.V Neuroleptic adverse reaction - Tremor**

**1)** Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**2)** Summary:
Effective in ameliorating psychotropic-induced tremor in case reports

**3)** Adult:
**a)** Within 3 to 7 days of beginning olanzapine 10 milligrams daily, 3 patients experienced remission of their persistent fluphenazine- or haloperidol-induced coarse tremors (Strauss et al, 1998). Two of the patients previously had unsuccessful trials of diphenhydramine, benztropine, amantadine and propranolol.

**4.5.W Obsessive-compulsive disorder, Refractory**

**1)** Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**2)** Summary:
Partially effective as an augmentation strategy with serotonin-reuptake inhibitors in studies with small numbers of patients
One study showed no additional benefit in the addition of olanzapine to fluoxetine therapy in the treatment of patients with fluoxetine-refractory obsessive-compulsive disorder

**3)** Adult:
**a)** GENERAL INFORMATION:
**1)** Information regarding the efficacy of olanzapine for the treatment of patients with refractory obsessive-compulsive disorder is contradictory. Uncontrolled studies with small numbers of patients have reported that olanzapine therapy (1.25 to 20 milligrams (mg)/day) is partially effective as an augmentation strategy with selective serotonin-reuptake inhibitors (SSRI), while the findings of a controlled study indicated that olanzapine (5 to 10 mg/day) offers no additional benefit when added to SSRI therapy in patients with fluoxetine-refractory obsessive compulsive disorder. Larger, controlled studies are needed to determine the role of olanzapine as an augmentation therapy in this patient population (Shapira et al, 2004); (Koran, et al, 2000; Weiss et al, 1999; Potenza et al, 1998).

**b)** The addition of olanzapine to ongoing fluoxetine therapy did not provide additional benefit in the treatment of patients with obsessive- compulsive disorder refractory to fluoxetine. In a double-blind, placebo-controlled study, patients (n=44) with obsessive-compulsive disorder of at least moderate severity who were partial or non- responders to 8 weeks of open-label treatment with fluoxetine (up to 40 milligrams (mg)/day) received add-on therapy with either olanzapine (initial, 5 mg/day, titrated up to 10 mg/day) or placebo for 6 weeks. Mean scores for the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) significantly improved for patients in both the fluoxetine-plus- olanzapine (decrease of 5.1) and fluoxetine-plus-placebo (decrease of 3.8) groups (p less than 0.0001). However, the treatment x time interaction was not significant for olanzapine (mean, 6.1 mg) versus placebo (mean, 5.9 mg) addition to fluoxetine. In each of the treatment groups, 9 (41%) patients showed a 25% or greater improvement in Y-BOCS score. In addition, a 35% or greater improvement was seen in 5 (23%) patients in the fluoxetine-plus-olanzapine group and in 4 (18%) patients in the fluoxetine-plus-placebo group. Combination treatment with olanzapine and fluoxetine was generally well tolerated, however patients receiving add-on

therapy with olanzapine gained more weight as compared with patients receiving placebo (mean, 2.8 kilograms vs 0.5 kilograms, respectively) (Shapira et al, 2004).

**c)** Olanzapine augmentation was partially effective in the treatment of 10 patients with obsessive-compulsive disorder unresponsive to fluoxetine therapy (60 milligrams per day (mg/d) for at least 10 weeks). Olanzapine 2.5 mg/d was added and titrated to 10 mg daily over 4 weeks as needed, and continued for an additional 4 weeks. Patients were assessed for improvement of symptoms using the Yale-Brown Obsessive-Compulsive Scale (YBOCS). A response to therapy was defined as a greater than or equal to 25% decrease in YBOCS score. Three patients responded, one was considered to be "very much improved" and 2 only minimally improved. Seven of 10 patients had comorbid conditions, including major depression, dysthymia, social phobia, avoidant personality disorder, and schizotypal personality disorder with tics. Two patients with comorbid conditions showed improvement: one with major depression showed markedly improved mood symptoms but not OCD, and another patient with dysthymia and OCD showed rapid improvement in both disorders. The most common adverse effects were weight gain, drowsiness, dry mouth, and increased appetite (Koran, et al, 2000).

**d)** Olanzapine may be effective in augmenting selective serotonin reuptake inhibitor (SSRI) treatment for some patients experiencing obsessive-compulsive disorder (OCD) refractory to SSRI therapy. Ten patients diagnosed with OCD and who had completed at least 12 weeks of SSRI therapy at adequate doses were given open- label olanzapine augmentation for a minimum of 8 additional weeks. Prior to initiating olanzapine, 6 of 10 patients had shown no improvement at the end of SSRI treatment and only 4 demonstrated a partial response. Olanzapine augmentation was initiated at 1.25 or 2.5 milligrams/day and titrated as indicated (mean dose was 7.3 +/- 7.3 milligrams/day). Within 8 weeks, 4 patients were responders and 3 were partial responders. Two patients experienced no changes in their OCD symptoms. Symptomatic improvement generally began within the first 2 weeks of olanzapine treatment. Therapy was generally well tolerated with 2 patients discontinuing olanzapine due to sedation. Further studies are warranted to determine the efficacy of olanzapine augmentation to SSRI therapy in the treatment of SSRI-refractory OCD (Weiss et al, 1999).

**e)** A 24-year-old woman with refractory obsessive-compulsive disorder benefited from the addition of olanzapine to her fluoxetine therapy (Potenza et al, 1998). She had previously failed a trial of clomipramine with risperidone. She was being maintained on fluoxetine 80 milligrams (mg) daily with a Yale-Brown Obsessive Compulsive Scale (YBOCS) score of 18. Olanzapine was titrated up to 20 mg daily over 3 months. After 4 weeks at that dose, her YBOCS score decreased to 10. She has maintained this response for 6 months, however, she has gained 18 pounds.

**4.5.X Parkinson's disease - Psychotic disorder**

**1)** Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**2)** Summary:

Decreases psychotic symptoms in nondemented, Parkinson's patients with drug-induced psychosis
May also worsen Parkinsonian symptoms

See Drug Consult reference: THERAPY OF PSYCHOTIC DISTURBANCES IN PARKINSONIAN PATIENTS

**3)** Adult:

**a)** The results of a prospective, open-label, uncontrolled study of 21 elderly patients (mean age 74.4 +/- 6.4 years) with advanced Parkinson's disease concluded olanzapine improved delusions and hallucinations while not worsening parkinsonism or cognition. The starting dose of olanzapine was 5 milligrams/day. Due to frequent side effects (primarily drowsiness), the starting dose was reduced to 2.5 milligrams/day. The maximum dosage was 10 milligrams/day. After 8 weeks of treatment, the summed score of the Neuropsychiatric Inventory (NPI) for delusions, hallucinations, and agitation

decreased by 85%, and 80% of those who completed the 8 weeks were considered much or very much improved, according to the final Clinical Global Impression (CGI) scores. Twenty-nine percent of patients withdrew due to side effects (primarily drowsiness). Larger controlled clinical trials are needed (Aarsland et al, 1999).

**b)** In a case series of patients suffering hallucinations and vivid dreams secondary to treatment of their parkinsonian symptoms, patients' psychotic symptoms improved, however, their motor symptoms declined (Graham et al, 1998a). Five outpatients with idiopathic Parkinson's disease with significant hallucinations were started on olanzapine 5 milligrams (mg) nightly. Two patients were increased to 7.5 mg. Hallucinations and vivid dreams declined; however, 2 patients had to discontinue olanzapine while the other 3 also had declines in their motor function and "on" time. The authors speculate that the motor decline would not have been as problematic if a smaller initial dosage form were available (less than 5 mg).

**c)** Olanzapine was well-tolerated and effective in an open study of 15 Parkinson's disease patients with drug-induced dopaminomimetic psychosis (DSM IV Criteria) (Wolters et al, 1996a). The initial dose was 1 milligram (mg) daily, titrated up to a maximum of 15 mg/day. Patients were assessed weekly using the Brief Psychiatric Rating Scale (BPRS), the Unified Parkinson's Disease Rating Scale (UPDRS), and a sleep somnologue. Olanzapine significantly reduced BPRS scores by 65% (p less than 0.05), significantly reduced UPDRS total scores by 21% (p less than 0.01), and increased total sleep time by 45% (p less than 0.01).

**d)** In a letter to the editor, one physician's experiences with olanzapine, in patients with drug-induced psychosis with akinetic rigid syndromes including Parkinson's disease, were not encouraging (Friedman, 1998). He described only 9 of 19 patients remaining on olanzapine and being a treatment success. The other 10 all experienced worsening of their parkinsonism despite 7 patients also improving in their psychoses. More studies are needed.

**4.5.Y Pervasive developmental disorder**

**1)** Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence is inconclusive

Recommendation: Adult, Class IIb; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**2)** Summary:

Some improvement in one small open-label study in patients with autism or pervasive developmental disorder not otherwise specified

Only 3 of 12 pediatric patients benefited in a small open-label trial

**3)** Adult:

**a)** In a 12-week open-label pilot study of eight children, adolescents, and adults with pervasive developmental disorders, six patients treated with olanzapine were rated as much improved or very much improved on the Clinical Global Impression Scale. Patients ranged in age from 5 to 42 years and met DSM-IV criteria for pervasive developmental disorder (autistic disorder, N=5; not otherwise specified, N=3). Mean olanzapine doses were 8 milligrams per day. Significant changes from baseline were observed on the Vineland Maladaptive Behavior Scale, Rivto-Freeman Real-life Rating Scale, Self-Injurious Behavior Questionnaire, and portions of the Clinician-Rated Visual Analog Scale (all p less than 0.001). One patient dropped out at week 9 due to lack of efficacy, six patients experienced weight gain, and three patients reported sedation (Potenza et al, 1999).

**4)** Pediatric:

**a)** A retrospective chart review demonstrated that olanzapine therapy (2.5 to 15 milligrams per day (mg/d)) was effective in reducing hyperactivity, aggression, and hallucinations in only 3 of 12 pediatric patients (aged 5 to 17 years) with developmental disabilities or psychotic disorders. Teachers or parents determined efficacy reporting improvement or worsening of symptoms. Ten of the 12 studied had previously failed other psychotropic medications. Seven patients were mentally retarded. Eight of the 12

children discontinued olanzapine after a mean duration of 50 days due to adverse effects (6), lack of positive effects (5), and exacerbated target symptoms or a combination of these issues (2). The most frequent side effects were an increased appetite and sedation. Slurred speech, tremulousness, drooling, and suicidal ideation were also reported (Demb & Roychoudhury, 2000). In another short-term study, 2 of 4 children discontinued olanzapine due to weight gain despite a positive response to therapy, while adult responders continued therapy without incident, suggesting that different age groups may exhibit diverse responses to olanzapine treatment (Potenza & McDougle, 2001).

**b)** In a 12-week open-label pilot study of eight children, adolescents, and adults with pervasive developmental disorders, six patients treated with olanzapine were rated as much improved or very much improved on the Clinical Global Impression Scale. Patients ranged in age from 5 to 42 years and met DSM-IV criteria for pervasive developmental disorder (autistic disorder, N=5; not otherwise specified, N=3). Mean olanzapine doses were 8 milligrams per day. Significant changes from baseline were observed on the Vineland Maladaptive Behavior Scale, Rivto-Freeman Real-life Rating Scale, Self-Injurious Behavior Questionnaire, and portions of the Clinician-Rated Visual Analog Scale (all p less than 0.001). One patient dropped out at week 9 due to lack of efficacy, six patients experienced weight gain, and three patients reported sedation (Potenza et al, 1999).

**4.5.Z Posttraumatic stress disorder**

**1)** Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**2)** Summary:

Improved all types of symptoms of PTSD in combat veterans
Effective in reducing sleep disturbance and nightmares secondary to PTSD in one case report

**3)** Adult:

**a)** Adjunctive olanzapine therapy was more effective than placebo in the treatment of patients with selective serotonin reuptake inhibitor (SSRI)-resistant posttraumatic stress disorder (PTSD). In a randomized, double-blind, placebo-controlled study, patients with combat-related PTSD who were minimally responsive to at least 12 weeks of SSRI treatment received 8 weeks of adjunctive therapy with either placebo (n=9) or olanzapine (n=10; initial, 10 milligrams (mg)/day then titrated to 20 mg/day as necessary; mean dose, 15 mg/day). Concurrent SSRI medications included fluoxetine (median dose 40 mg/day), paroxetine (median dose 40 mg/day), and sertraline (median dose 200 mg/day). Olanzapine-treated patients showed significantly greater reductions in PTSD symptoms (p less than 0.05), sleep disturbances (p=0.01), and depressive symptoms (p less than 0.03) as compared with placebo. However, response rates for clinical global improvement were not significantly different between the two treatment groups. Patients treated with olanzapine gained significantly more weight during treatment as compared with placebo (mean, 13.2 pounds (lb) vs -3 lb, respectively; p=0.001). In this regard, the authors note that the benefits of olanzapine as an adjunctive treatment to an SSRI should be weighed against the potential health risks associated such a large weight gain (Stein et al, 2002).

**b)** Olanzapine treatment improved all outcome measures of post- traumatic stress syndrome (PTSD) in a group of combat veterans with a DSM-IV diagnosis of PTSD. In an 8-week, open-label, uncontrolled study, all patients (n=46) were initially given olanzapine 5 milligram (mg) per day. The dosage could be increased in 5 mg/week increments to a maximum of 20 mg/day. Mean dose at study end was 14 mg/day. By the end of treatment, scores on the Clinician Administered PTSD Scale (CAPS) decreased by approximately 30%. Symptom clusters were reduced: intrusive by 31%, avoidant by 31%, and hyperarousal by 28%. Adverse event included increased appetite (49%), dry mouth (45%), insomnia (23%), weight gain (22%), drowsiness (22%), blurred vision (18%), headache (13%), dizziness (10%), constipation (10%), and tremor (10%). Only 30 patients completed the study (Petty et al, 2001).

**c)** Nightmares and hallucinations experienced by a 58-year-old male combat veteran with posttraumatic

stress disorder (PTSD) ceased within 1 week after initiation of olanzapine therapy (5 milligrams at bedtime). The patient, who had a 20-year history of PTSD had been treated for anxiety, depression, and sleep disturbances with psychotherapy and numerous psychotropics including amitriptyline, imipramine, doxepin, diazepam, diphenhydramine, cyproheptadine, fluoxetine, bupropion, sertraline, and trazodone. Although his depression and anxiety improved, nightmares and hallucinations persisted. The patient's mood and anxiety were reasonably well controlled with sertraline 200 mg daily (QD), bupropion 150 mg QD, and diazepam 15 mg QD. Once olanzapine was added to this regimen, sleep quality improved after 2 nights. A trial dose of 10 mg caused daytime drowsiness and hangover, so the 5 mg dose was continued. Nightmares did not recur during the next 4 months (Labbate, 2000).

**4.5.AA Repetitive self-excoriation**

**1)** Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
**2)** Summary:
Effective in self-induced dermatoses in isolated cases
**3)** Adult:
**a)** Self-excoriation of acne lesions was significantly reduced in a 28-year-old high school teacher by treatment with olanzapine. The woman had had acne since age 14 and had begun excoriating her acne at age 16. At age 18 her acne was successfully treated with isotretinoin. However, it recurred a year later, during a time of stress, and she resumed self- excoriation. Under stress at age 28 and performing excoriation, she was given olanzapine 2.5 milligrams at bedtime. Improvement in her excoriating behavior was evident in 2 weeks, with further improvement at 4 weeks. She continued the treatment for 6 months and started psychotherapy. As of 4 months after the discontinuation of olanzapine, she had maintained the improvement (Gupta & Gupta, 2002).
**b)** Three patients with self-inflicted dermatoses were successfully treated with olanzapine 2.5 to 5 milligrams (mg) daily. Patients exhibited healing of excoriated acne, self-induced skin ulcers, and trichotillomania within 2 to 4 weeks of initiating olanzapine therapy. Duration of therapy varied from 3 to more than 6 months. Improvement was maintained in 1 patient by taking 2.5 mg once or twice weekly as required (Gupta & Gupta, 2000).

**4.5.AB Schizophrenia**

FDA Labeled Indication
**1)** Overview
FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
**2)** Summary:
Indicated for the management of psychotic disorders
Produced significant reductions in both positive and negative symptoms in SCHIZOPHRENIC and SCHIZOPHRENIFORM patients
Effective for positive and negative symptoms of schizophrenia in Japanese patients
**3)** Adult:
**a)** GENERAL INFORMATION
**1)** Oral olanzapine has produced significant reductions in both positive and negative symptoms in SCHIZOPHRENIC and SCHIZOPHRENIFORM patients in uncontrolled and placebo-controlled

studies, with a low propensity for extrapyramidal effects (Prod Info Zyprexa(R), 2000a); (Tolleson et al, 1998; Beasley et al, 1996)(Anon, 1995; Anon, 1994b; Anon, 1994aa). The drug has been more effective than haloperidol for improving negative symptoms on some scales (Beasley et al, 1996)(Anon, 1995). In one review of medical records, olanzapine was more likely to be effective in patients that were younger, female, and also have a diagnosis of bipolar disorder (Zarate et al, 1998). In 1 case, it was successfully used for the short-term treatment of psychotic symptoms associated with coproporphyria (Strauss & DiMartini, 1999).

**b)** SHORT-TERM STUDIES

**1)** Olanzapine and risperidone were equally safe and effective therapies in the treatment of schizophrenia in elderly patients. In an international, multicenter, double-blind study, 175 elderly patients (mean age, 71 years) were randomized to receive either risperidone (mean dose, 1.9 milligrams (mg)/day) or olanzapine (mean dose, 11.1 mg/day) for 8 weeks following a 1 week washout period of all psychotropic medications. Mean duration of illness was 36.5 years and Positive and Negative Syndrome Scale (PANSS) scores were between 50 and 120 at baseline. Clinical improvement was defined as a decrease of at least 20% in the total PANSS score. Both treatment groups showed significant reductions from baseline in the total PANSS score at all time points (p less than 0.005) and significant differences were not observed between groups. Fifty-eight percent of risperidone-treated patients and 59% of olanzapine-treated patients achieved clinical improvement as defined by the study. Both groups also exhibited significant improvement in four of the five PANSS factor scores (p less than 0.001). The greatest mean change in the total PANSS score occurred in the 93 patients who had received conventional antipsychotic medications in the thirty days prior to entering the study (p less than 0.001). The rate of extrapyramidal symptoms (EPS) was similar between the risperidone and olanzapine treatment groups (9.2% vs 15.9%, respectively, p=ns). The severity of EPS symptoms was reduced in both groups from baseline to endpoint with no significant difference between groups. A 7% or higher increase in weight occurred in significantly more olanzapine-treated patients as compared with those who received risperidone (14.8% vs 5.1%, p=0.043). No new cardiovascular events were observed in this patient population and mean QT-c changes were not considered clinically relevant (Jeste et al, 2003a).

**2)** Olanzapine was safe and effective for the treatment of schizophrenia in Japanese patients. Eighty-one patients meeting the International Classification of Diseases, 9th edition, criteria for schizophrenia were given olanzapine 1 milligram (mg) per day to a maximum of 12.5 mg/day for 8 weeks, with an optional 4 week extension. The mean dose during the study was 7.9 mg/day. Prior to the study, 67% of patients had been using anticholinergic medications, whereas during the study, only 14% used anticholinergics, suggesting that the frequency or severity of extrapyramidal symptoms was lower with olanzapine than with their prior antipsychotic medications. Moderate and remarkable improvement was seen in 59% of the patients. The Weekly Brief Psychiatric Rating Scale showed statistically significant improvement (p less than 0.05) from week 1 to week 8 on total score, anxiety- depression, and anergia; from week 2 to week 9 on activation and thought disturbances; and from week 4 to week 8 on hostility. The most commonly reported adverse effects were insomnia, weight increase, excitement, sleepiness, and anxiety. Serum prolactin levels, which were high at baseline, were reduced by study endpoint (Ishigooka et al, 2001a).

**3)** In one case report, high doses (40 milligrams/day) of olanzapine appeared to be more effective for treatment-resistant schizophrenia than olanzapine 20 milligrams/day (Alao, 2000). The patient, who had a history of schizophrenia, initiated olanzapine therapy at a dose of 10 milligrams twice daily. This dose was continued for 3 weeks with no significant clinical improvement. The dose was then increased to 40 milligrams/day and within 6 days the patient noted improvements in thought process, agitation, and behavior. Additionally, there was no evidence of extrapyramidal symptoms associated with the higher dose. Complete blood counts, liver function tests, electrocardiogram, vital signs, and clinical evaluations were also normal. More studies are needed to distinguish the benefits and weaknesses of high-dose olanzapine therapy in treatment- resistant schizophrenia.

**4)** Olanzapine combined with sulpiride, a selective dopamine-2-receptor blocker, significantly improved symptoms of chronic, treatment-resistant schizophrenia (n=5) and acute psychosis (n=1). Olanzapine doses were titrated to 20 milligrams (mg) daily (QD) in 4 patients and 40 mg QD in 2

others. Sulpiride doses ranged from 60 to 600 mg QD. Treatment response, defined by improvement in the Brief Psychiatric Rating Scale (BPRS), the Positive and Negative Syndrome Scale (PANSS), and the Clinical Global Impression Scale (CGI), occurred between 2 and 6 weeks after initiation of therapy. No adverse effects were reported (Raskin et al, 2000).

**5)** Five patients who experienced refractory psychosis attributed to noncompliance with clozapine therapy due to adverse effects were subsequently able to tolerate olanzapine therapy (Weiss, 1999). On admission, all patients were drug-free, highly symptomatic, and had a mean Brief Psychiatric Rating Scale (BPRS) score of 47. At discharge, all patients were responding well to olanzapine treatment (10 to 20 milligrams/day) and had a mean BPRS score of 17. Upon interview, 2 patients reported mild dizziness and weight gain, while 1 patient reported akathisia. More studies are needed to confirm the use of olanzapine in patients with treatment-refractory psychosis who are intolerant of clozapine.

**6)** A successful transition from clozapine to olanzapine was attained in 8 out of 19 schizophrenic or schizophreniform patients receiving a stable dose of clozapine (Henderson et al, 1998). In an open study, olanzapine 5 milligrams (mg) daily was added to each patient's regimen and increased by 2.5 to 5 mg weekly to a maximum of 30 mg/day. After the first week, clozapine doses were gradually decreased by increments of 25 to 50 mg per week. A successful transition was defined as maintaining a stable clinical status on olanzapine treatment alone for at least 2 weeks. Baseline clozapine dose was 372 mg/day and mean final olanzapine dose was 17.1 mg/day. Eight patients successfully transitioned, 7 patients decompensated seriously enough to require hospitalization, and an additional 4 patients showed worsening of clinical status. Scores on the Brief Psychiatric Rating Scale increased with significant increases for the negative symptoms subscale (p=0.002) and the depressive symptoms subscale (p=0.04). The 8 patients that responded did have their clinical status stabilize after 4 to 8 weeks. Those that responded had been treated for a significantly shorter period of time with clozapine (p=0.04) and were receiving a lower dose of clozapine (p=0.05).

**7)** In an open study, some patients with refractory schizophrenia or schizoaffective disorder responded to olanzapine doses greater than 20 milligrams (mg)/day (Fanous & Lindenmayer, 1999). Seven treatment-refractory patients received olanzapine titrated over 14 weeks to 30 mg. A 30% reduction in the Brief Psychiatric Rating Scale was achieved at a dose of 25 mg in 3 of 7 patients; they had only achieved a 20% reduction at 20 mg. A reduction of 29% was achieved by a fourth patient at 30 mg/day while only attaining a 14% reduction at lower doses. Only 1 patient had an improvement of 36% at 20 mg/day. Three of the 4 responders were also receiving typical neuroleptics. The 2 nonresponders were receiving no other medications. The high doses were well-tolerated with only weight gain and diarrhea reported as adverse effects.

**8)** In an open trial of olanzapine in 16 patients with treatment-refractory psychosis, only two patients showed significant improvement (Clinical Global Improvement score of 1 to 3) over the 12 week study period. Patients were between 31 and 49 years old and had a mean duration of illness of 18 years. All patients had failed therapy with at least 2 antipsychotics previously and were taken off all psychotropics, with the exception of benzodiazepines and a single patient taking valproic acid. Two patients were taken off olanzapine after one week; one due to mania and hallucinations and the second due to assaultive behavior and paranoia. Two additional patients did not finish 12 weeks of treatment. Based on the Positive and Negative Symptoms Score and Clinical Global Impression scale, no significant changes were seen over the 12 week period. Mean daily benzodiazepine use increased (p=0.002) over the study period; however, benztropine use decreased (p less than 0.05). No patient discontinued olanzapine due to side effects (Sanders & Mossman, 1999).

**9)** Olanzapine showed a superior and broader spectrum of efficacy over haldol in the treatment of schizophrenia and also had a more favorable safety profile (Tollefson et al, 1998a; Tollefson et al, 1997b). In a large international, multicenter double-blind trial, olanzapine (N=1336) was compared to haloperidol (N=660) over 6 weeks. Starting doses were 5 milligrams (mg) for both drugs which could be increased by 5 mg increments at the investigators discretion to a maximum of 20 mg/day. Olanzapine was significantly superior to haldol on the Brief Psychiatric Rating Scale (p less than 0.02), the Positive and Negative Syndrome Scale (p=0.05), the Clinical Global Impression severity score (p less than 0.03), and the Montgomery-Asberg Depression Rating Scale total score (p=0.001). Significant advantages were also seen in the extrapyramidal profiles and effects on prolactin levels.

This study's methods were subsequently criticized (Capehart & Holsinger, 1998; Barbui, 1998; Mattes, 1998). Some of the criticisms included: no specific information on study participants, mismatched doses of haloperidol and olanzapine, and questionable blinding procedures.

**10)** In an open, pilot study, olanzapine was effective and well-tolerated in neuroleptic-resistant patients (Martin et al, 1997). Schizophrenic patients (subtypes: 18 paranoid type, 4 disorganized, 3 undifferentiated) with a documented lack of response to 2 conventional antipsychotic agents entered a 6-week study with olanzapine 15 to 25 milligrams. At the end of the study, the patients showed a statistically significant improvement over baseline in both positive and negative symptoms (p less than 0.05). Overall 35% of the patients met the criteria for treatment-response (greater than 35% decrease or a total score of less than 18 on the Brief Psychiatric Rating Scale and a rating of less than 3 on the Clinical Global Impression-Severity scale). One case report also documents the effectiveness of olanzapine in a patient that was treatment-resistant to typical neuroleptic medications and unable to tolerate clozapine due to tachycardia (Thomas & Labbate, 1998).

**11)** With olanzapine in mean doses of 11.6 and 16.3 milligrams daily for a period of 6 weeks, reductions in total Brief Psychiatric Rating Scale (BPRS) scores by 13 and 15 (from baseline of approximately 42), respectively, were reported in schizophrenic patients (primarily chronic schizophrenia with acute exacerbation) in a relatively large trial (n=335). For positive symptoms (BPRS-positive), such as conceptual disorganization, hallucinations, and suspiciousness, both doses were of similar efficacy (decreased by 4.5 points), whereas the higher dose tended to be more effective for negative symptoms (BPRS-negative) (-3 versus -1.4 points), including emotional withdrawal and motor retardation. The Scale for Assessment of Negative Symptoms (SANS) also revealed trends for the superiority of the higher dose. Although decreases in the BPRS-total and BPRS-positive scores were statistically significant compared to placebo, significance was achieved for negative symptoms on both SANS and BPRS-negative only with the higher dose (16.3 milligrams/day). A lower dose of olanzapine (mean, 6.6 milligrams/day) did, however, result in significant reductions in negative symptoms on both scales; this suggests a flaw in the trial or the need for additional dose-ranging studies. The percentage of patients demonstrating improvement on the BPRS-total scale (eg, 40% improvement, 80% improvement) did not always reach a level of significance for olanzapine over placebo (Beasley et al, 1996).

**12)** In a placebo-controlled study (n=152), olanzapine 10 milligrams (mg) daily was significantly superior to placebo in improving overall symptoms (Brief Psychiatric Rating Scale total and Positive and Negative Syndrome Scale (PANSS) total scores) in chronic schizophrenic patients who were primarily refractory to prior therapy. Some patients had shown refractoriness to clozapine (Beasley et al, 1996aa). In this trial, 10 mg daily doses of olanzapine were also superior to placebo with regard to core psychotic symptoms (PANSS positive scores and PANSS negative scores). A dose of olanzapine 1 mg daily was comparable to placebo on all measures of efficacy.

**c)** LONG-TERM STUDIES

**1)** Olanzapine is also approved for long-term therapy and maintenance treatment of schizophrenia. Authors of a double-blind, placebo-controlled study concluded that olanzapine demonstrated efficacy and long-term safety in the maintenance treatment response in schizophrenia. Outpatients (n=326) with stable schizophrenia or schizoaffective disorder were randomized to receive olanzapine (10 to 20 milligrams daily) or placebo. The patients receiving olanzapine improved on all quality of life measures while the patients receiving placebo worsened. Olanzapine was safe and well tolerated at all doses (10, 15 or 20 milligrams daily) (Anon, 2000).

**2)** Two other studies were presented that demonstrated olanzapine's superiority to placebo and to a subtherapeutic olanzapine dose (1 milligram) in the maintenance therapy of schizophrenia (Dellva & Tran Tollefson, 1997). In a 46 week double-blind, multicenter study, patients who met DSM-III-R criteria for schizophrenia with an acute exacerbation and who had previously responded to acute therapy were enrolled. In the first study, patients received either olanzapine (n=45) or placebo (n=13), and in the second study patients received either olanzapine (n=48) or a subtherapeutic dose of olanzapine (n=14). In the first study, patients in the olanzapine group experienced a significantly lower relapse risk (p equal to 0.002) than the placebo group. In the second study, patients in the olanzapine group again experienced a significantly lower relapse risk (p equal to 0.018) than the group treated

with a subtherapeutic dose of olanzapine.

**4.5.AC Schizophrenia, Refractory**

**1)** Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
**2)** Summary:
Improved symptoms sufficiently for hospital discharge in about half of patients in small study
May be effective in the treatment of children with drug-resistant childhood-onset schizophrenia
**3)** Adult:
**a)** Among patients who had been hospitalized for schizophrenia for longer than 5 years and who were considered treatment- refractory, approximately 45% showed sufficient clinical improvement after 3 months of treatment with olanzapine or risperidone to be discharged from the hospital. The 79 patients were not suited to treatment with clozapine either because of medical contraindications or because of unwillingness to submit to the weekly blood drawings. Patients were given olanzapine 10 to 30 milligrams (mg) per day or risperidone 4 to 10 mg/day. Treatments were titrated quickly to the maximum tolerated dose and continued for 3 months. Mean scores on the Brief Psychiatric Rating Scale decreased from 67 to 53 for the olanzapine group (n=32) and from 63 to 52 for the risperidone group (n=47) (p less than 0.001 for both groups). Of the 34 patients who were discharged from the hospital, only 3 required rehospitalization during the 90-day follow-up. No significant side effects (such as weight change) were observed during the 3 months (Dinakar et al, 2002).
**4)** Pediatric:
**a)** Olanzapine seemed to be effective in the treatment of children with drug-resistant schizophrenia. In an open-label study, nine patients, 11 to 14 years of age (mean age, 12.5 years), with childhood-onset schizophrenia refractory to previous treatment with at least two typical antipsychotics received olanzapine (initial, 2.5 milligrams (mg)/day, titrated to doses of 10, 15, or 20 mg per day; mean dose, 15.56 mg/day) for 12 weeks following a 2-week washout period. Significant reductions were observed at week 12 as compared with baseline in the mean scores for the Brief Psychotic Rating Scale (decreased from, 54.89 vs 37.3; p=0.03) and the Clinical Global Impression scale (decreased from 6.09 to 4.7; p less than 0.005). The Positive and Negative Syndrome Scale (PANSS) total mean score was reduced from 123.56 at baseline as compared with 96.7 at week 12 (p=0.026). In addition, the positive and negative syndrome scores showed significant reductions at week 12 as compared with baseline (p=0.048 and p=0.05, respectively). The most common adverse effects included somnolence (77%) and weight gain (100%; mean weight gain, 6.1 kilograms). No extrapyramidal side effects, dystonias, elevated hepatic transaminase levels, blood abnormalities, electrocardiogram or electroencephalogram abnormalities were observed. Larger, controlled studies are needed to further establish the safety and efficacy of olanzapine for the treatment of childhood-onset schizophrenia (Mozes et al, 2003).

**4.5.AD Schizophrenic prodrome**

**1)** Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
**2)** Summary:
May be effective in the treatment schizophrenic prodromal syndrome
**3)** Adult:

**a)** The results of one study suggest that olanzapine may be effective in the treatment of patients experiencing prodromal symptoms of schizophrenia. In a randomized, double-blind, placebo-controlled, multicenter study, patients with prodromal syndrome received olanzapine 5 to 15 milligrams (mg) daily (n=31; mean dose, 8 mg/day) or placebo (n=29) for 8 weeks. Results of the study were inconsistent across analyses. In a mixed effects analysis of the data, olanzapine-treated patients showed a significant improvement from baseline to endpoint in total score for the Scale of Prodromal Symptoms (SOPS) (treatment x time interaction), as compared with placebo (p less than 0.005). However, when a last observation carried forward (LOCF) analysis was done, the trend favored olanzapine but did not reach statistical significance. Significantly more patients taking olanzapine experienced a weight gain of more than 7% of their baseline body weight as compared with placebo (56.7% vs 3.4%, respectively, p less than 0.001). Larger, longer-term studies are needed in order to establish clinical efficacy (Woods et al, 2003).

**4.5.AE Senile dementia** of the Lewy body type

**1)** Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**2)** Summary:
Effective in low doses (5 milligrams/day) but not at high doses (15 mg/day)

**3)** Adult:

**a)** Olanzapine at low doses significantly reduced delusions and hallucinations in patients with **dementia** with Lewy bodies (DLB). The patients with DLB (n=29) were a subset of patients with Alzheimer's disease being treated for psychosis with various doses of olanzapine in a randomized, double- blind, placebo-controlled trial. Within the DLB subset, 10 patients were treated with placebo, 5 with olanzapine 5 milligrams (mg) per day, 7 with olanzapine 10 mg/day, and 7 with olanzapine 15 mg/day. In comparison to scores with placebo treatment, final scores on the delusions subscale of the Neuropsychiatry Inventory-Nursing Home (NPI/NH) after 12 weeks of olanzapine treatment were significantly better for the 5 mg group (p=0.009) and the 10 mg group (p=0.018) but not for the 15 mg group. Scores on the hallucinations subscale were significantly better for the 5 mg group only. Olanzapine did not cause any significant exacerbation of symptoms of parkinsonism or any decrease in cognition. The 5-mg dose also diminished disruptiveness of patients (Cummings et al, 2002).

**b)** Olanzapine (2.5 to 7.5 milligrams daily) showed little advantage over conventional neuroleptics in 8 patients diagnosed with **Dementia** with Lewy bodies (DLB). Only 2 patients demonstrated clear improvement in psychotic and behavioral symptoms. Three patients gained only minimal clinical benefit and the remaining 3 patients could not tolerate olanzapine, even at the lowest dose. The data suggests that benzodiazepines, antidepressants, and sociopsychological methods should be considered prior to olanzapine for treatment of DLB (Walker et al, 1999).

**4.5.AF Severe major depression with psychotic features**

See Drug Consult reference: PSYCHOTIC DEPRESSION - DRUG THERAPY

**4.5.AG Tardive dyskinesia**

**1)** Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**2)** Summary:
Improvements seen in tardive dyskinesias after switching to olanzapine in case reports
See Drug Consult reference: TARDIVE DYSKINESIA - DRUG THERAPY

**3)** Adult:

**a)** Tardive dyskinesia improved in 2 patients after being switched to olanzapine (Soutullo et al, 1999a). The first patient had an initial score of 26 on the Abnormal Involuntary Movement Scale (AIMS) which improved after 4 weeks. His AIMS score was 9 at 2 months, 6 at 9 months, and 8 after 11 months. He was maintained on olanzapine 15 milligrams (mg). The second had a score of 31 which improved to 3 after 1 week. At 4 months he continued olanzapine 20 mg with a score of 9. Other cases of significant improvement have been reported (Almeida, 1998).

**b)** Four cases of patients with tardive dyskinesias showing marked improvements on the Abnormal Involuntary Movement Scale have been reported (Littrell et al, 1998). All cases involved patients on long-term neuroleptic therapy that were switched to olanzapine and titrated up to 20 milligrams. After 6 months of therapy tardive dyskinesias had decreased.

### 4.5.AH Trichotillomania

**1)** Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**2)** Summary:
Effective in several cases, either alone or as adjunct therapy with fluoxetine or citalopram
Effectively reduced symptoms of hair pulling during small, open-label trial
See Drug Consult reference: TRICHOTILLOMANIA - DRUG THERAPY

**3)** Adult:

**a)** Olanzapine therapy reduced symptoms of hair pulling, depression, and anxiety in patients with trichotillomania. In a prospective, open- label study, patients (n=17) diagnosed with trichotillomania received 12 weeks of treatment with olanzapine (initial, 2.5 milligrams (mg) at bedtime, titrated to maximum dose of 10 mg at bedtime by week 8; mean dose at week 12, 8.5 mg/day). A significant reduction in the mean score for the Massachusetts General Hospital Hairpulling Scale (MGH) was observed from baseline to weeks 4, 6, 8, and 12 (weeks 4 and 6, p less than or equal to 0.01; weeks 8 and 12, p less than or equal to 0.001). From baseline to endpoint, hair pulling was reduced by 66% (MGH), anxiety levels decreased by 63% as measured by the Hamilton Rating Scale for Anxiety (p less than or equal to 0.05) and depressive symptoms shrunk by 43% as measured by the Hamilton Rating Scale for Depression. The most common adverse events were sedation and weight gain. Randomized, controlled trials are needed to confirm these findings (Stewart & Nejtek, 2003).

**b)** In 3 of 4 patients with trichotillomania as well as other psychiatric disorders, olanzapine in addition to citalopram greatly reduced hair-pulling. In all 4 patients, trichotillomania had failed to respond to various regimens of SSRIs (selective serotonin reuptake inhibitors). Effective doses of olanzapine were 2.5, 5, and 7.5 milligrams (mg) per day. The dose used by the patient whose trichotillomania did not respond was 1.25 mg/day. Concurrent citalopram doses were 60 or 80 mg/day (Ashton, 2001).

**c)** Three patients with self-inflicted dermatoses were successfully treated with olanzapine 2.5 to 5 milligrams (mg) daily. Patients exhibited healing of excoriated acne, self-induced skin ulcers, and trichotillomania within 2 to 4 weeks of initiating olanzapine therapy. Duration of therapy varied from 3 to more than 6 months. Improvement was maintained in 1 patient by taking 2.5 mg once or twice weekly as required (Gupta & Gupta, 2000).

**d)** A 22-year-old woman with trichotillomania improved when olanzapine was added to her fluoxetine regimen (Potenza et al, 1998). The woman suffered from trichotillomania and obsessive-compulsive

disorder. She had failed trials with multiple selective serotonin reuptake inhibitors, lithium, desipramine, and perphenazine. She did have a response to fluvoxamine with risperidone but developed severe hyperprolactinemia. She received a 15-week trial of fluoxetine 40 milligrams (mg)/day and then had olanzapine 10 mg added. After 7 weeks, her Massachusetts General Hospital Hairpulling scale score decreased from 23 to 6 and the Yale-Brown Obsessive Compulsive Scale compulsion subscale from 13 to 4. Due to sedation, her olanzapine was decreased to 2.5 mg daily. Thereafter, she tolerated olanzapine well but gained 8 pounds.

## 4.6 Comparative Efficacy / Evaluation With Other Therapies

### 4.6.A Aripiprazole

#### 4.6.A.1 Schizophrenia

**a)** A trend toward greater improvement in some areas of neurocognitive function (eg, verbal learning, working memory) was reported for aripiprazole 30 mg daily compared to olanzapine 15 mg daily in a randomized study (n=256) (Kern et al, 2001). However, a placebo group was lacking, and details of this study are unavailable (unpublished).

### 4.6.B Chlorpromazine

#### 4.6.B.1 Schizophrenia

**a)** Based upon comparisons of minimum effective dosages identified in placebo-controlled, fixed-dose and fixed-dose-ranging drug development trials in schizophrenic patients, the minimum effective dose of olanzapine was 10 milligrams/day (equivalent to chlorpromazine 200 milligrams/day) (Woods SW, 2003).

#### 4.6.B.2 Schizophrenia, Treatment-resistant

**a)** Olanzapine 25 milligrams (mg) daily and chlorpromazine 1200 mg daily plus benztropine 4 mg daily showed similarly modest effects in an 8-week randomized trial of 84 patients with treatment-resistant schizophrenia. No significant differences were seen between the groups on the Brief Psychiatric Rating Scale (BPRS), Scale for the Assessment of Negative Symptoms, or the Clinical Global Impression (CGI) Score. Only 7% (n=3) of olanzapine patients and none of the chlorpromazine patients met response criteria of at least a 20% reduction in baseline BPRS score and a post-treatment CGI score of less than 3 or a post-treatment BPRS score of less than 35. Dry mouth, orthostatic changes, and unsteady gait were more common among chlorpromazine patients (p less than 0.01), as was extrapyramidal symptoms (p less than 0.05) (Conley et al, 1998).

### 4.6.C Clozapine

#### 4.6.C.1 Bipolar disorder

**a)** In a retrospective study of 50 consecutive patients treated for bipolar disorder with atypical antipsychotic medications, clozapine (n=5), olanzapine (n=20), and risperidone (n=25), along with standard mood stabilizers, showed similar efficacy. Overall, 68% of patients showed improvement of at least 1 point in their Clinical Global Impressions assessment over the 12-week study. Mean dosages were 210 milligrams (mg) per day for clozapine, 11.7 mg/day for olanzapine, and 1.7 mg day for risperidone. The only serious adverse event to occur during the study was a seizure in a patient taking clozapine. Extrapyramidal symptoms (EPS) were reported in 12 of 42 subjects (28.6%). Parkinsonism

occurred in 4 of 25 patients taking risperidone, 1 of 20 taking olanzapine, and 1 of 5 taking clozapine. Weight gain was more extreme in patients taking clozapine and olanzapine than in those taking risperidone. Weight gain, which was greater than reported in other studies, may have been affected by concurrent mood enhancing medications (Guille et al, 2000a).

**4.6.C.2 Drug-induced psychosis**

**a)** In a small (n=18), open study, clozapine and olanzapine were both effective in reducing symptoms of dopaminergic drug-induced psychosis in patients with Parkinson's disease. However, olanzapine and not clozapine caused worsening of Parkinsonian symptoms. The starting dose of clozapine was 6.25 to 25 milligrams (mg) per day and was increased at weekly intervals as necessary to optimize clinical status. The final mean dose of clozapine at the end of the 8-week study was 16.9 mg /day (range: 6.25 to 37.5 mg/day). Olanzapine was started at 2.5 to 5 mg/day. The final mean dose of olanzapine for the 6 patients completing the study was 4.7 mg/day (range: 2.5 to 10 mg/day). Three patients dropped out of the study after receiving the starting dose of olanzapine (2.5 mg for 2 patients, 5 mg for 1 patient) because of worsening of parkinsonism. All patients in the clozapine group completed the study, despite side effects of somnolence, falls, orthostatic hypotension, and syncope. Neuropsychiatric symptoms markedly improved with both medications (72% and 65% reduction in Neuropsychiatric Inventory global scores for clozapine and olanzapine, respectively). Parkinsonian motor scores (raw scores) improved by 20% in the clozapine group and worsened by 25% in the olanzapine group. It is possible that the differences observed were due to non-equivalence of the doses and that the dosage of olanzapine was excessive (Gimenez-Roldan & Mateo D Navarro, 2001).

**4.6.C.3 Hostile behavior**

**a)** Clozapine reduced hostility in patients with schizophrenia and was superior to haloperidol and risperidone in that regard. One hundred fifty seven patients with a diagnosis of schizophrenia or schizoaffective disorder and a history of poor response to drug treatment were randomly assigned to receive clozapine, olanzapine, risperidone, or haloperidol in cross-titration with the antipsychotic drug used prior to the start of the study. Concomitant mood stabilizers and antidepressants had been phased out earlier. Daily doses of olanzapine, risperidone, and haloperidol were escalated within the first week to the target doses of 20, 8, and 20 milligrams (mg), respectively. Patients receiving clozapine were scheduled to achieve the target daily dose of 500 mg on day 24. Doses remained fixed for the remainder of the initial 8-week period. In a second (6-week) period, doses were allowed to vary: 200 to 800 mg for clozapine, 10 to 40 mg for olanzapine, 4 to 16 mg for risperidone, and 10 to 30 mg for haloperidol. Hostility, measured by the hostility item of the Positive and Negative Syndrome Scale (PANSS), improved significantly (in comparison to baseline) in the clozapine group only (p=0.019). This effect was independent of effects on psychotic symptoms (delusional thinking, hallucinations) or on sedation. The effect of clozapine on hostility was superior to that of haloperidol (p=0.021) or risperidone (p=0.012) but not to that of olanzapine (Citrome et al, 2001).

**4.6.C.4 Schizophrenia**

**a)** Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine in patients with schizophrenia or schizoaffective disorder that was refractory to treatment with typical antipsychotics. In a randomized, double-blind study, inpatients were given clozapine (n=24) 200 to 800 milligrams (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26) 4 to 16 mg day, or haloperidol (n=25) 10 to 30 mg/day. Dose escalation and fixed-dose treatment (target doses: olanzapine 20 mg/day, risperidone 8 mg/day, haloperidol 20 mg/day, clozapine 500 mg/day) occurred during the first 8 weeks of the 14-week study; during the last 6 weeks, dosages were adjusted individually (generally increased if response was insufficient, but sometimes reduced because of adverse effects). Improvement over time in global neurocognitive score was seen for olanzapine and risperidone. In

general executive and perceptual organization and in processing speed and attention, improvement was seen with olanzapine. In simple motor function, there was improvement with clozapine. Changes in global neurocognitive performance with olanzapine and risperidone were of medium magnitude (approximately 8 to 9 "IQ equivalents") but large enough to be clinically significant. Beneficial changes with clozapine were modest. Despite cognitive gains, patients still had significant impairments of cognitive ability and social/vocational functioning. Improvements in neurocognitive deficits were associated with improvements in negative symptoms (Bilder et al, 2002b).

**4.6.C.5 Schizophrenia - Suicidal intent**

**a)** In the International Suicide Prevention Trial (InterSePT), clozapine was shown to be more effective than olanzapine in reducing suicidal behavior in high-risk, adult, patients with schizophrenia or schizoaffective disorder. Men and women between the ages of 18 to 65 years, at high risk of committing suicide, were recruited to participate in this 2-year, prospective, randomized, international, parallel group, study. The endpoints in this study included significant suicide attempts (including completed suicides) or hospitalization due to imminent suicide risk (type 1 events) or ratings of "much worse" or "very much worse" on the Clinical Global Impression of Suicide Severity (CGI-SS) scale (type 2 events). Of the total sample of 980 patients enrolled in the study, 62% (609) were diagnosed as having schizophrenia and 38% (371) were diagnosed with schizoaffective disorder. Twenty-seven percent (263) of these patients were considered treatment resistant. The patients were divided into two treatment groups (clozapine or olanzapine) and did not differ significantly in terms of age, sex, race, diagnosis, treatment resistance, number of previous suicide attempts, or baseline concomitant medications. Both groups had weekly or biweekly clinical contact. Dropout rates for the two groups were similar with 192 discontinuing treatment with clozapine and 187 with olanzapine. Clozapine showed a hazard ratio of 0.76 (95% CI, 0.58-0.97) for type 1 events (p=.03) and 0.78 (95% CI, 0.61-0.99) for type 2 events (p=.04) compared to olanzapine. The most frequently reported adverse events for the olanzapine group were weight gain, somnolence, dry mouth, and dizziness, while salivary hypersecretion, somnolence, weight gain, and dizziness were the most frequently reported adverse events reported for the clozapine group. The overall number of adverse events did not differ significantly between the two groups. Decreased white blood cell counts occurred in 5.8% of clozapine-treated patients and in 0.8% of olanzapine-treated patients, but there were no reports of agranulocytosis or deaths due to granulocytopenia in either group. There was a total of 8 suicide deaths in the two groups (5 clozapine and 3 olanzapine). The mean daily olanzapine dosage was 16.6 +/- 6.4 mg and the mean daily clozapine dosage was 274.2 +/- 155.0 mg (Meltzer et al, 2003).

**4.6.C.6)** Adverse Effects

**a)** The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence of PANCREATITIS than patients receiving a conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of pancreatitis were identified in patients taking clozapine (mean dose, 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), risperidone, (mean dose, 4 mg/day) or haloperidol (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications clozapine, olanzapine, or risperidone, respectively, as compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol. In most patients, time to onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003b).

**b)** Results of a retrospective analysis showed that olanzapine treatment was associated with a lower rate of extrapyramidal symptoms (EPS) than haloperidol, but was similar to rates occurring with risperidone and clozapine therapy. In a pooled analysis of 23 randomized, controlled clinical trials in 4611 patients with schizophrenia, frequency and severity of EPS associated with olanzapine therapy (2.5 to 20 milligrams (mg)/day) was compared with that of haloperidol (1 to 20 mg/day), risperidone (4 to 12 mg/day), clozapine (25 to 625 mg/day), and placebo. Dystonic events (ie, dystonia, oculogyric crisis, opisthotonos, torticollis) occurred in significantly fewer patients during olanzapine treatment as compared with haloperidol (0.5% vs 5.6%, respectively; p less than 0.001) or risperidone (1% vs 3.2%,

respectively; p=0.047) treatment, while no significant difference was found between olanzapine- and clozapine-treated patients. As compared with olanzapine-treated patients, a significantly higher percentage of haloperidol-treated patients experienced parkinsonian events (ie, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, and tremor) (9.3% vs 28.3%, respectively; p less than 0.001) or akathisia events (ie, akathisia, hyperkinesia) (6.7% vs 20.4%, respectively; p less than 0.001) during therapy. However, no significant difference was observed between the olanzapine group as compared with the placebo, risperidone, or clozapine groups in regard to the occurrence of parkinsonian or akathisia events. Overall, EPS occurred in significantly more patients treated with haloperidol as compared with olanzapine (44.4% vs 16.2%, respectively; p less than 0.001) and in fewer patients treated with clozapine as compared with olanzapine (2.6% vs 6.8%, respectively; p=0.047). The overall rate of EPS was similar between the placebo and risperidone groups as compared with olanzapine. Significantly fewer patients received anticholinergic medications in the olanzapine group as compared with the haloperidol (p less than 0.001) or risperidone (p=0.018) groups. No difference was found between olanzapine-treated patients as compared with placebo or clozapine in regard to percentage of patients given anticholinergic drugs during therapy (Carlson et al, 2003b).

**c)** In an open-label trial (n=24), olanzapine-treated patients had significantly lower levels of serum anticholinergic activity than clozapine-treated patients. Prior to enrollment, subjects were stabilized on therapeutic doses, averaging 15 milligrams (mg)/day and 444 mg/day for olanzapine and clozapine, respectively. The mean serum anticholinergic levels were 0.96 and 5.47 picomoles/atropine equivalents in the olanzapine and clozapine groups, respectively (p less than 0.001). Scores assessing clinical anticholinergic effects were significantly higher for salivation, constipation, micturition disturbances and palpitations/tachycardia in clozapine versus olanzapine recipients (p less than 0.05). Dry mouth was more problematic with olanzapine therapy (p less than 0.0008). The groups did not differ cognitively with respect to Mini Mental State Exam scores. Although efficacy was not a primary endpoint, the Brief Psychiatric Rating Scale scores favored clozapine (p=0.002), with no statistical difference in Clinical Global Impression Scale, Severity subscale scores. No patients in either group discontinued therapy due to adverse effects (Chengappa et al, 2000).

### 4.6.D Haloperidol

#### 4.6.D.1 Adverse reaction to cannabis - Drug-induced psychosis

**a)** Olanzapine was as effective as haloperidol in the treatment of cannabis-induced psychotic disorder (Berk et al, 1999). In a double- blind study, patients with a psychotic episode associated with cannabis use were randomized to receive either olanzapine 10 milligrams (n=15) or haloperidol 10 mg (n=15). After 4 weeks there was a significant improvement in both groups as compared to baseline measured on the Brief Psychiatric Rating Scale (p=0.0002 for olanzapine, p=0.0001 for haloperidol). There was no significant difference between the 2 groups. Olanzapine was associated with fewer extrapyramidal side effects.

#### 4.6.D.2 Mania

**a)** Olanzapine and haloperidol therapies were similarly effective in the treatment of acute mania in patients with bipolar disorder. In a randomized, double-blind study, patients with bipolar I disorder, mixed or manic episode and a Young-Mania Rating Scale (Y-MRS) score of at least 20 received either olanzapine (5 to 20 milligram (mg)/day) or haloperidol (3 to 15 mg/day) at flexible doses for 6 weeks. Patients showing symptom improvement entered a 6-week continuation phase in which they received ongoing treatment. Symptomatic remission was defined as a Y-MRS score of 12 or less and a Hamilton Rating Scale for Depression score (HAM-D) of 8 or less at week 6. Symptomatic remission rates for patients in the olanzapine group were similar to those of patients in the haloperidol group at week 6 (52.1% vs 46.1%, respectively; p=NS) and week 12 (51.7% vs 43.8%, respectively; p=NS). However, olanzapine treatment produced greater improvements in health- related quality of life factors as compared

with haloperidol treatment (Shi et al, 2002).

**4.6.D.3 Schizophrenia**

**a)** SUMMARY: Olanzapine is more effective than haloperidol for the treatment of negative symptoms of schizophrenia; both agents are similarly effective in managing positive symptoms. Olanzapine is less likely to induce extrapyramidal reactions or elevation of serum prolactin levels.
**b)** Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine in patients with schizophrenia or schizoaffective disorder that was refractory to treatment with typical antipsychotics. In a randomized, double-blind study, inpatients were given clozapine (n=24) 200 to 800 milligrams (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26) 4 to 16 mg day, or haloperidol (n=25) 10 to 30 mg/day. Dose escalation and fixed-dose treatment (target doses: olanzapine 20 mg/day, risperidone 8 mg/day, haloperidol 20 mg/day, clozapine 500 mg/day) occurred during the first 8 weeks of the 14-week study; during the last 6 weeks, dosages were adjusted individually (generally increased if response was insufficient, but sometimes reduced because of adverse effects). Improvement over time in global neurocognitive score was seen for olanzapine and risperidone. In general executive and perceptual organization and in processing speed and attention, improvement was seen with olanzapine. In simple motor function, there was improvement with clozapine. Changes in global neurocognitive performance with olanzapine and risperidone were of medium magnitude (approximately 8 to 9 "IQ equivalents") but large enough to be clinically significant. Beneficial changes with clozapine were modest. Despite cognitive gains, patients still had significant impairments of cognitive ability and social/vocational functioning. Improvements in neurocognitive deficits were associated with improvements in negative symptoms (Bilder et al, 2002).
**c)** Olanzapine was at least as effective as and safer than haloperidol for the treatment of schizophrenia in a large population of Japanese patients with positive and negative symptoms resistant to treatment with typical antipsychotics. In a randomized, double-blind trial, 182 patients were given olanzapine, starting at 5 milligrams (mg) per day and increased to a maximum of 15 mg/day, or haloperidol, starting at 4 mg/day and increasing to 12 mg/day, for 8 weeks. Mean modal daily doses were 10.5 mg for olanzapine and 8 mg for haloperidol. The proportion of olanzapine-treated patients who showed moderate to remarkable improvement was 44.5%, compared to 40.5% of haloperidol-treated patients. The 95% confidence interval was -8% to 16% favoring olanzapine. Thus, olanzapine was not inferior to haloperidol in efficacy. Total and subscale scores on the Positive and Negative Symptom Scale (PANSS) were numerically better in the olanzapine group than in the haloperidol group, but only on the negative symptoms subscale did the difference reach statistical significance (p=0.024). Eighty-one percent of olanzapine-treated patients and 66% of haloperidol-treated patients finished the study, with fewer dropping out of the olanzapine group because of adverse events or abnormal laboratory values ( 8 vs 22). Olanzapine-treated patients showed an improvement in extrapyramidal symptoms, whereas haloperidol-treated patients showed a worsening (p less than 0.001). Treatment-emergent parkinsonism occurred in 3.2% of the olanzapine group and 18.8% of the haloperidol group. By the end of treatment, parkinsonism had resolved in all patients in the olanzapine group but was sustained in 7.8% of the haloperidol group. There was a significantly greater incidence of insomnia, akathisia, tremor, anorexia, increased salivation, bradykinesia, abnormal gait, nausea, and weight decrease in haloperidol-treated patients than in olanzapine-treated patients. Only weight gain was significantly greater with olanzapine (0.96 kilogram vs -0.71 kilogram, p less than 0.001). Thirty-two percent of olanzapine-treated patients showed no adverse drug reaction and no laboratory abnormality, compared to 15.5% of haloperidol-treated patients (p=0.008) (Ishigooka et al, 2001).
**d)** Olanzapine has been at least as effective as haloperidol, each given for six weeks, in the treatment of schizophrenia (Tollefson et al, 1997); (Beasley et al, 1996)(Anon, 1996; Anon, 1995). Overall improvement, based on Brief Psychiatric Rating Scale (BPRS) total scores, has been greater with olanzapine; this reached significance in the largest trial (Anon, 1996). Both agents have produced similar decreases in positive symptoms, and the superior overall improvement with olanzapine is attributed to a greater reduction in negative symptoms in these patients, particularly in higher dosages (12.5 to 17.5 mg daily); decreases in negative symptoms have been significantly greater with olanzapine on the Scale for

the Assessment of Negative Symptoms (SANS) and Positive and Negative Syndrome Scale (PANSS), although significance was not achieved on the BPRS-negative scale in one study (Beasley et al, 1996). Significantly more patients have demonstrated greater than 80% improvement in BPRS-total scores with olanzapine, whereas the percentage with lower levels of improvement has not always differed significantly between drugs.

**e)** Intramuscular (IM) olanzapine successfully treated acutely agitated patients with schizophrenia in 3 clinical trials. Two open-label, single-blind trials evaluated 108 patients receiving fixed or variable doses of 2.5, 5.0, 7.5, or 10.0 milligram (mg) given as 1 to 4 injections daily (QD) for 3 days, followed by 10 to 20 mg orally (PO) QD for 2 days. Response was assessed using the Brief Psychiatric Rating Scale (BPRS); the positive subscale improved during both IM and PO Administration (no statistical analysis was performed). The third study was a multicenter, double-blind, placebo-controlled trial that compared IM olanzapine with IM haloperidol in the treatment of acute agitation. Patients (n=311) received up to 3 doses of olanzapine (10 mg), haloperidol (7.5 mg) or placebo in 24 hours. Thereafter, patients were treated with oral olanzapine (5 to 20 mg QD) or oral haloperidol (5 to 20 mg QD) for 4 days. Patients treated with IM olanzapine or haloperidol showed significantly greater improvement over placebo at 2 and 24 hours as measured by the BPRS positive subscale, but no differences were observed between olanzapine- and haloperidol-treated patients. Patients treated with intramuscular olanzapine continued to improve to day 5; but, there was no significant difference between patients treated with IM drug between baseline and day 5 (Jones et al, 2000)

**f)** In a study of 300 patients with schizoaffective disorder, olanzapine treated patients showed significantly greater improvement than haloperidol treated patients on the Brief Psychiatric Rating Scale (BPRS) total (p=0.002), Positive and Negative Syndrome Scale (PANSS) total (p=0.003), PANSS negative (p=0.006), and Montgomery-Asberg Depression Rating Scale (MADRS) total (p less than 0.001). Patients were taken from a larger prospective, double blind study. Patients were assessed weekly for a six week acute phase with responders followed for up to 1-year. Among acute phase patients with bipolar subtype, olanzapine (5 to 20 milligrams) was superior to haloperidol (5 to 20 milligrams) in the BPRS (p=0.012), PANSS negative (p=0.031) and total (p=0.028), and MADRS (p less than 0.001); however, in depressed subtype patients, no significant differences were seen when compared to haloperidol treated patients. During the double-blind extension phase, the only significant difference between treatment groups was in the MADRS total score in favor of olanzapine (p=0.045). Extrapyramidal symptoms were less severe among olanzapine treated patients (p=0.016), but weight gain was more problematic (p=0.032) (Tran et al, 1997).

**g)** In a 6-week randomized study of 83 patients with first-episode psychosis (schizophrenia, schizophreniform disorder, or schizoaffective disorder), patients receiving olanzapine showed significantly greater improvement on the Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Symptoms Scale (PANSS) as compared to patients receiving haloperidol. Patients greater than 45 years of age at onset of symptoms with a disease duration of greater than 5 years received olanzapine or haloperidol 5 milligrams (mg) per day and adjusted every 7 days within the range of 5 to 20 mg per day. On the BPRS, 67.2% of olanzapine treated patients experienced a 40% or greater improvement from baseline compared to 29.2% of haloperidol treated patients (p=0.003). Olanzapine treated patients also improved more on the PANSS total score (p=0.02) and positive symptom score (p=0.03) compared to haloperidol treated patients. Using the Simpson-Angus scale, olanzapine patients showed improvement in extrapyramidal symptoms, whereas haloperidol treated patients worsened (p less than 0.001). Somnolence was more common in olanzapine treated patients, whereas akathisia and hypertonia were more common with haloperidol (Sanger et al, 1999).

**h)** Olanzapine showed a superior and broader spectrum of efficacy over haloperidol in the treatment of schizophrenia and also had a more favorable safety profile (Tollefson et al, 1997). In a large international, multicenter double-blind trial, olanzapine (N=1336) was compared to haloperidol (N=660) over 6 weeks. Starting doses were 5 milligrams (mg) for both drugs which could be increased by 5 mg increments at the investigator's discretion to a maximum of 20 mg/day. Olanzapine was significantly superior to haloperidol on the Brief Psychiatric Rating Scale (p less than 0.02), the Positive and Negative Syndrome Scale (p=0.05), the clinical Global Impression severity score (p less than 0.03), and the Montgomery-Asberg Depression Rating Scale total score (p=0.001). Significant advantages were also

seen in the extrapyramidal profiles and effects on prolactin levels. Further analyses revealed that depressive signs and symptoms were also better controlled with olanzapine therapy (Tollefson et al, 1998). On the Montgomery-Asberg Depression Rating Scale, olanzapine was significantly more effective than haloperidol (p = 0.001).

**i)** In multiple clinical trials of olanzapine, the incidence of self-directed aggression among patients receiving olanzapine, haloperidol, or placebo, was not significantly different (Keck et al, 2000a). These trials indicated a significantly greater improvement in suicidal thoughts in olanzapine-treated patients compared with haloperidol-treated patients. Another analysis demonstrated a 2.3-fold reduction in the annual suicide attempt rate among chronic psychotic patients receiving olanzapine versus haloperidol.

**4.6.D.4 Tardive dyskinesia**

**a)** Olanzapine was associated with a lower incidence of tardive dyskinesia when compared to haloperidol (Tollefson, 1997a). Data combined from 3 controlled and blinded studies evaluating patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder treated with olanzapine (n=707) or haloperidol (n=197) were compared. Patients had no evidence of tardive dyskinesia at baseline. At any visit after baseline 7.1% of patients in the olanzapine group and 16.2% of patients in the haloperidol group manifested treatment-emergent tardive dyskinesia (p less than 0.001). At the last study visit, 2.3% of olanzapine patients and 7.6% of haloperidol patients manifested tardive dyskinesia (p equal to 0.001). Similar results have been reported (Beasley et al, 1999).

**4.6.D.5)** Efficacy

**a)** Results of a retrospective analysis showed that olanzapine treatment was associated with a lower rate of extrapyramidal symptoms (EPS) than haloperidol, but was similar to rates occurring with risperidone and clozapine therapy. In a pooled analysis of 23 randomized, controlled clinical trials in 4611 patients with schizophrenia, frequency and severity of EPS associated with olanzapine therapy (2.5 to 20 milligrams (mg)/day) was compared with that of haloperidol (1 to 20 mg/day), risperidone (4 to 12 mg/day), clozapine (25 to 625 mg/day), and placebo. Dystonic events (ie, dystonia, oculogyric crisis, opisthotonos, torticollis) occurred in significantly fewer patients during olanzapine treatment as compared with haloperidol (0.5% vs 5.6%, respectively; p less than 0.001) or risperidone (1% vs 3.2%, respectively; p=0.047) treatment, while no significant difference was found between olanzapine- and clozapine-treated patients. As compared with olanzapine-treated patients, a significantly higher percentage of haloperidol-treated patients experienced parkinsonian events (ie, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, and tremor) (9.3% vs 28.3%, respectively; p less than 0.001) or akathisia events (ie, akathisia, hyperkinesia) (6.7% vs 20.4%, respectively; p less than 0.001) during therapy. However, no significant difference was observed between the olanzapine group as compared with the placebo, risperidone, or clozapine groups in regard to the occurrence of parkinsonian or akathisia events. Overall, EPS occurred in significantly more patients treated with haloperidol as compared with olanzapine (44.4% vs 16.2%, respectively; p less than 0.001) and in fewer patients treated with clozapine as compared with olanzapine (2.6% vs 6.8%, respectively; p=0.047). The overall rate of EPS was similar between the placebo and risperidone groups as compared with olanzapine. Significantly fewer patients received anticholinergic medications in the olanzapine group as compared with the haloperidol (p less than 0.001) or risperidone (p=0.018) groups. No difference was found between olanzapine-treated patients as compared with placebo or clozapine in regard to percentage of patients given anticholinergic drugs during therapy (Carlson et al, 2003).

**b)** Pooled safety results from 3 large double-blind, controlled trials in 2606 patients demonstrated that olanzapine had a significantly lower rate of any extrapyramidal symptoms (EPS) occurring versus haloperidol (p less than 0.001) (Tran et al, 1997). Also statistically fewer patients treated with olanzapine discontinued the study because of EPS (p less than 0.001). This suggests that the use of olanzapine may be associated with better long-term compliance due to fewer adverse effects.

**c)** The risk of extrapyramidal adverse effects is lower with olanzapine compared to haloperidol, especially dystonic reactions. Increases in serum prolactin have been significantly less with olanzapine (Tollefson et al, 1997); (Beasley et al, 1996)(Anon, 1996; Anon, 1995).

**4.6.D.6)** Adverse Effects

**a)** The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence of PANCREATITIS than patients receiving a conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of pancreatitis were identified in patients taking clozapine (mean dose, 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), risperidone, (mean dose, 4 mg/day) or haloperidol (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications clozapine, olanzapine, or risperidone, respectively, as compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol. In most patients, time to onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003).

**4.6.E Lithium**

**4.6.E.1 Mania**

**a)** A review of 3 randomized, double-blinded, placebo-controlled studies concluded that a more rapid antimanic effect was achieved with olanzapine or oral loading of divalproex than with standard titration divalproex, lithium or placebo. In these short-term studies, oral-loaded divalproex (n=80) was either initiated at 30 milligrams/kilogram/day (mg/kg/day) for the first 2 days and maintained at 20 mg/kg/day or it was initiated at 20 mg/kg/day for the first 2 days and gradually increased to a maximum of 20 mg/kg/day plus 1000 mg by day 6. This regimen was compared to divalproex (n=87) initiated at 250 mg 3 times daily and titrated to serum levels of 40 to 150 micrograms/milliliter (mcg/mL), lithium (n=54) initiated at 300 mg 3 times a day and titrated to 0.4 to 1.5 milliequivalents per liter, and olanzapine (n=55) initiated at 10 mg/day and titrated to a maximum of 20 mg/day and placebo (n=72). Patients were followed for 10 days and efficacy was assessed using the change from baseline measurement of the Mania Rating Scale (MRS), the Manic Syndrome Scale (MSS) and the Behavior and Ideation Scale (BIS). Intent-to-treat analyses showed that MRS measurements from oral-loaded divalproex patients were not significantly different from olanzapine patients. However, it showed significant differences from standard titration divalproex and placebo by day 5 and from lithium by days 7 to 8 (p less than 0.02). Similar results were found for MSS and BIS measurements. Dry mouth and increased appetite was more commonly reported with divalproex load compared to standard titration (p less than 0.05). However, standard titration divalproex was associated with an increased incidence of dizziness, general pain and back pain (p less than 0.05). Divalproex overall was associated with greater decreases in platelet counts than other groups (p less than 0.05). Lithium was associated with greater reports of headache and fever (p less than 0.05) and olanzapine was associated with greater adverse events (such as dry mouth, weight gain, edema, speech disorder, rhinitis, increases in total cholesterol and increases in serum alanine aminotransferase) overall (p less than 0.05) (Hirschfeld et al, 2003).

**b)** Olanzapine was found to be at least as effective as lithium in the treatment of mania. In a 4-week, double-blind trial, 30 patients with acute manic episodes were randomized to receive olanzapine 10 milligrams daily or lithium carbonate 400 milligrams twice daily. There were no significant differences between the two treatment groups on any primary outcome measures. However, olanzapine was significantly (p equal to 0.025) superior to lithium for improving the Clinical Global Impression severity scale at week 4 (lithium 2.83, olanzapine 2.29). The two medications did not differ in terms of treatment emergent extrapyramidal symptoms (Berk et al, 1999a).

**4.6.F Olanzapine/Fluoxetine Hydrochloride**

**4.6.F.1 Depression - Schizophrenia**

**a)** Results of an 8-week, double-blind trial demonstrated that patients receiving both olanzapine and fluoxetine in combination demonstrated greater improvement in Montgomery-Asberg Depression Rating Scale (MADRS) and Clinical Global Impression (CGI) total scores than patients receiving either

medication alone. Twenty-eight patients with nonpsychotic treatment-refractory depression received olanzapine (5 to 20 milligrams/day) and/or fluoxetine (20 to 60 milligrams/day). In addition, there were no significant differences in adverse events among the 3 different treatment groups (Keck et al, 2000).

**4.6.G Perphenazine**

**4.6.G.1 Chronic schizophrenia**

**a)** When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

**4.6.H Quetiapine**

**4.6.H.1 Chronic schizophrenia**

**a)** When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

**4.6.I Risperidone**

**4.6.I.1 Bipolar disorder**

**a)** In a retrospective study of 50 consecutive patients treated for bipolar disorder with atypical antipsychotic medications, clozapine (n=5), olanzapine (n=20), and risperidone (n=25), along with standard mood stabilizers, showed similar efficacy. Overall, 68% of patients showed improvement of at least 1 point in their Clinical Global Impressions assessment over the 12-week study. Mean dosages were 210 milligrams (mg) per day for clozapine, 11.7 mg/day for olanzapine, and 1.7 mg day for risperidone. The only serious adverse event to occur during the study was a seizure in a patient taking

clozapine. Extrapyramidal symptoms (EPS) were reported in 12 of 42 subjects (28.6%). Parkinsonism occurred in 4 of 25 patients taking risperidone, 1 of 20 taking olanzapine, and 1 of 5 taking clozapine. Weight gain was more extreme in patients taking clozapine and olanzapine than in those taking risperidone. Weight gain, which was greater than reported in other studies, may have been affected by concurrent mood enhancing medications (Guille et al, 2000).

**4.6.I.2 Chronic schizophrenia**

**a)** When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

**4.6.I.3 Dementia** - Problem behavior

**a)** Risperidone and olanzapine were equally effective in the treatment of dementia-related behavioral disturbances in elderly patients at long- term care facilities. In a double-blind, parallel study, patients (mean age, 83 years) with **dementia** received oral olanzapine (n=20, initial dose, 2.5 milligrams (mg)/day, titrated to maximum dose of 10 mg/day) or risperidone (n=19, initial dose 0.5 mg/day, titrated to maximum dose of 2 mg/day) at bedtime for two weeks following a 3-day washout period of psychotropic drugs. Antidepressants and mood stabilizers were allowed at stable doses and lorazepam was used as a rescue medication at doses of 0.5 to 1 mg as needed for acute agitation. The mean daily doses for olanzapine and risperidone were 6.65 mg (range, 2.5 to 10 mg) and 1.47 mg (range, 0.5 to 2 mg), respectively. Lorazepam was utilized a median of 3.5 days (range 1-12 days) and the median dose was 2 mg (range, 0.2 to 21 mg). Primary outcome measures were the Neuropsychiatric Inventory (NPI) and the Clinical Global Impressions Scale (CGI). Both treatments significantly lowered CGI scores and total NPI scores from baseline to endpoint (p less than 0.0001, both values), however, there was no difference between the two groups. Adverse events were frequent in this elderly population, with the most common including drowsiness, falls, and extrapyramidal symptoms (Fontaine et at, 2003).

**4.6.I.4 Extrapyramidal disease**

**a)** Results of a retrospective analysis showed that olanzapine treatment was associated with a lower rate of extrapyramidal symptoms (EPS) than haloperidol, but was similar to rates occurring with risperidone and clozapine therapy. In a pooled analysis of 23 randomized, controlled clinical trials in 4611 patients with schizophrenia, frequency and severity of EPS associated with olanzapine therapy (2.5 to 20 milligrams (mg)/day) was compared with that of haloperidol (1 to 20 mg/day), risperidone (4 to 12 mg/day), clozapine (25 to 625 mg/day), and placebo. Dystonic events (ie, dystonia, oculogyric crisis, opisthotonos, torticollis) occurred in significantly fewer patients during olanzapine treatment as compared with haloperidol (0.5% vs 5.6%, respectively; p less than 0.001) or risperidone (1% vs 3.2%, respectively; p=0.047) treatment, while no significant difference was found between olanzapine- and clozapine-treated patients. As compared with olanzapine-treated patients, a significantly higher

percentage of haloperidol-treated patients experienced parkinsonian events (ie, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, and tremor) (9.3% vs 28.3%, respectively; p less than 0.001) or akathisia events (ie, akathisia, hyperkinesia) (6.7% vs 20.4%, respectively; p less than 0.001) during therapy. However, no significant difference was observed between the olanzapine group as compared with the placebo, risperidone, or clozapine groups in regard to the occurrence of parkinsonian or akathisia events. Overall, EPS occurred in significantly more patients treated with haloperidol as compared with olanzapine (44.4% vs 16.2%, respectively; p less than 0.001) and in fewer patients treated with clozapine as compared with olanzapine (2.6% vs 6.8%, respectively; p=0.047). The overall rate of EPS was similar between the placebo and risperidone groups as compared with olanzapine. Significantly fewer patients received anticholinergic medications in the olanzapine group as compared with the haloperidol (p less than 0.001) or risperidone (p=0.018) groups. No difference was found between olanzapine-treated patients as compared with placebo or clozapine in regard to percentage of patients given anticholinergic drugs during therapy (Carlson et al, 2003a).

**4.6.I.5 Schizophrenia**

**a)** Olanzapine and risperidone were equally safe and effective therapies in the treatment of schizophrenia in elderly patients. In an international, multicenter, double-blind study, 175 elderly patients (mean age, 71 years) were randomized to receive either risperidone (mean dose, 1.9 milligrams (mg)/day) or olanzapine (mean dose, 11.1 mg/day) for 8 weeks following a 1 week washout period of all psychotropic medications. Mean duration of illness was 36.5 years and Positive and Negative Syndrome Scale (PANSS) scores were between 50 and 120 at baseline. Clinical improvement was defined as a decrease of at least 20% in the total PANSS score. Both treatment groups showed significant reductions from baseline in the total PANSS score at all time points (p less than 0.005) and significant differences were not observed between groups. Fifty-eight percent of risperidone-treated patients and 59% of olanzapine-treated patients achieved clinical improvement as defined by the study. Both groups also exhibited significant improvement in four of the five PANSS factor scores (p less than 0.001). The greatest mean change in the total PANSS score occurred in the 93 patients who had received conventional antipsychotic medications in the thirty days prior to entering the study (p less than 0.001). The rate of extrapyramidal symptoms (EPS) was similar between the risperidone and olanzapine treatment groups (9.2% vs 15.9%, respectively, p=ns). The severity of EPS symptoms was reduced in both groups from baseline to endpoint with no significant difference between groups. A 7% or higher increase in weight occurred in significantly more olanzapine-treated patients as compared with those who received risperidone (14.8% vs 5.1%, p=0.043). No new cardiovascular events were observed in this patient population and mean QT-c changes were not considered clinically relevant (Jeste et al, 2003).
**b)** Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine in patients with schizophrenia or schizoaffective disorder that was refractory to treatment with typical antipsychotics. In a randomized, double-blind study, inpatients were given clozapine (n=24) 200 to 800 milligrams (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26) 4 to 16 mg day, or haloperidol (n=25) 10 to 30 mg/day. Dose escalation and fixed-dose treatment (target doses: olanzapine 20 mg/day, risperidone 8 mg/day, haloperidol 20 mg/day, clozapine 500 mg/day) occurred during the first 8 weeks of the 14-week study; during the last 6 weeks, dosages were adjusted individually (generally increased if response was insufficient, but sometimes reduced because of adverse effects). Improvement over time in global neurocognitive score was seen for olanzapine and risperidone. In general executive and perceptual organization and in processing speed and attention, improvement was seen with olanzapine. In simple motor function, there was improvement with clozapine. Changes in global neurocognitive performance with olanzapine and risperidone were of medium magnitude (approximately 8 to 9 "IQ equivalents") but large enough to be clinically significant. Beneficial changes with clozapine were modest. Despite cognitive gains, patients still had significant impairments of cognitive ability and social/vocational functioning. Improvements in neurocognitive deficits were associated with improvements in negative symptoms (Bilder et al, 2002a).
**c)** In a prospective, multicenter, double-blind trial, olanzapine was more cost-effective than risperidone in patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder. One hundred fifty

patients were randomized to either olanzapine (10 to 20 milligrams per day (mg/d) (n=75) or risperidone (4 to 12 mg/d) (n=75) treatment for a period of 28 weeks. During the study, olanzapine- treated patients were significantly more likely to maintain a therapeutic response throughout the course of therapy than risperidone- treated patients (p=0.048). However, the proportion of patients who responded to treatment was not significantly different between groups. Overall, the incidence of side effects was similar between groups, but significantly more risperidone-treated patients required an anticholinergic to control treatment-emergent extrapyramidal effects than did those receiving olanzapine (45% versus 25%, p=0.016). Medication costs were significantly higher for olanzapine-treated patients than those treated with risperidone ($2513 versus $1581 US), but this difference was offset by a 52% reduction in inpatient and outpatient service costs ($3516 vs $7291 US) (Edgell et al, 2000).

**d)** In an open-label study of patients with DSM-IV schizophrenia, olanzapine (n=21) was shown to be as effective as risperidone (n=21) as acute treatments. At 6 months, risperidone was more effective for treatment of psychotic symptoms. However, olanzapine was associated with less akathisia at the end of 6 months. At discharge the average doses of olanzapine and risperidone were 14.4 and 5.7 milligrams (mg) daily, respectively. The reduction of psychotic symptoms with resperidone was significantly greater than with olanazapine. The dose of drug was uncontrolled and adjusted by the treating psychiatrist based on the patient's response, tolerability of side effects, and manufacturer recommendations. Measures of effectiveness included the SANS, SAPS, Brief Psychiatric Rating Scale (BPRS), Global Assessment Scale (GAS) and quality of life measures. (Ho et al, 1999). Larger studies are needed comparing olanzapine and risperidone.

**e)** Olanzapine (10 to 20 milligrams (mg) daily) was superior to risperidone (4 to 12 mg daily) in the treatment of schizophrenic symptomology. In an international, multicenter, double-blind, parallel-group 28-week prospective study of 339 patients with DSM-iv criteria for schizophrenia, schizophreniform disorder, or schizo-affective disorder, the olanzapine group had a significantly better overall response rate (greater than 40% decrease in the Positive and Negative syndrome Scale) and was significantly superior to risperidone in the treatment of negative symptomatology. Based on the Kaplan-Meier survival curves, a significantly greater number of the olanzapine patients maintained their response at 28 weeks compared to the risperidone group. Overall adverse reactions were significantly less with olanzapine, in particular extrapyramidal side effects, hyperprolactinemia and sexual dysfunction, with the exception of weight gain; suicide attempts occurred significantly less in the olanzapine group (Tran et al, 1997a). The use of possibly unequivalent doses in this study has been subsequently criticized (Schooler, 1998; Gheuens & Grebb, 1998).

**4.6.I.6)** Adverse Effects

**a)** The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence of PANCREATITIS than patients receiving a conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of pancreatitis were identified in patients taking clozapine (mean dose, 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), risperidone, (mean dose, 4 mg/day) or haloperidol (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications clozapine, olanzapine, or risperidone, respectively, as compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol. In most patients, time to onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003a).

### 4.6.J Valproic Acid

#### 4.6.J.1 Mania

**a)** A review of 3 randomized, double-blinded, placebo-controlled studies concluded that a more rapid antimanic effect was achieved with olanzapine and oral loading of divalproex than with standard titration divalproex, lithium or placebo. In these short-term studies, oral-loaded divalproex (n=80) was either initiated at 30 milligrams/kilogram/day (mg/kg/day) for the first 2 days and maintained at 20 mg/kg/day or it was initiated at 20 mg/kg/day for the first 2 days and gradually increased to a maximum of 20

mg/kg/day plus 1000 mg by day 6. This regimen was compared to divalproex (n=87) initiated at 250 mg 3 times daily and titrated to serum levels of 40 to 150 micrograms/milliliter (mcg/mL), lithium (n=54) initiated at 300 mg 3 times a day and titrated to 0.4 to 1.5 milliequivalents per liter, and olanzapine (n=55) initiated at 10 mg/day and titrated to a maximum of 20 mg/day and placebo (n=72). Patients were followed for 10 days and efficacy was assessed using the change from baseline measurement of the Mania Rating Scale (MRS), the Manic Syndrome Scale (MSS) and the Behavior and Ideation Scale (BIS). Intent-to-treat analyses showed that MRS measurements from oral-loaded divalproex patients were not significantly different from olanzapine patients. However, it showed significant differences from standard titration divalproex and placebo by day 5 and from lithium by days 7 to 8 (p less than 0.02). Similar results were found for MSS and BIS measurements. Dry mouth and increased appetite was more commonly reported with divalproex load compared to standard titration (p less than 0.05). However, standard titration divalproex was associated with an increased incidence of dizziness, general pain and back pain (p less than 0.05). Divalproex overall was associated with greater decreases in platelet counts than other groups (p less than 0.05). Lithium was associated with greater reports of headache and fever (p less than 0.05) and olanzapine was associated with greater adverse events (such as dry mouth, weight gain, edema, speech disorder, rhinitis, increases in total cholesterol and increases in serum alanine aminotransferase) overall (p less than 0.05) (Hirschfeld et al, 2003a).

**b)** Olanzapine was superior to divalproex for the treatment of acute mania in a 3-week, randomized, double-blind study. Two hundred fifty one patients with bipolar I disorder, manic or mixed episode, and with or without psychotic features, were given flexibly dosed olanzapine (5 to 20 milligrams (mg) per day) or divalproex (500 to 2500 mg/day). Modal doses were 17.4 mg/day for olanzapine and 1401 mg/day for divalproex. A divalproex blood level of 50 microgram/liter (mcg/L) or greater (the targeted therapeutic range) was attained by approximately 87% of divalproex-treated patients. The mean improvement in the Young Mania Rating Scale total score was 13.4 points for the olanzapine group and 10.4 points for the divalproex group (p less than 0.03). In subgroup analysis, the difference was significant (in favor of olanzapine) among patients without psychotic features (p=0.06), but there was no difference between treatments among patients with psychotic features. Clinical response (50% or greater improvement in they Young Mania Rating Scale score) was achieved by 54% of olanzapine-treated patients and 43% of divalproex-treated patients (p=0.058). Time-to- remission was significantly shorter with olanzapine (3 days vs 6 days, p less than 0.04). There were more adverse events with olanzapine, mainly somnolence, dry mouth, and weight gain. Nausea occurred more frequently in the divalproex group (Tohen et al, 2002).

### 4.6.K Ziprasidone

#### 4.6.K.1 Chronic schizophrenia

**a)** When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

#### 4.6.K.2 Schizophrenia

**a)** In a randomized, double-blind trial (n=269), six-week courses of OLANZAPINE and ZIPRASIDONE had comparable efficacy for treatment of schizophrenia or schizoaffective disorder (DSM-IV), while the side effects profile of ziprasidone appeared to be more favorable with respect to metabolic indicators but less favorable related to QT interval prolongation. Enrollees were acutely ill, recently admitted inpatients. During the first week, subjects received fixed doses of study drugs: olanzapine 5 milligrams (mg) on days 1 and 2 and 10 mg/day on days 3 to 7 (n=133); ziprasidone 40 mg twice daily on days 1 and 2 and 80 mg twice daily on days 3 to 7 (n=136). Dosing was flexible over weeks 2-6 (olanzapine 5 to 15 mg/day; ziprasidone 40 to 80 mg twice daily); overall median daily doses were 12.4 mg for olanzapine and 138.6 mg for ziprasidone (the latter in 2 divided doses daily). Efficacy measures included the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI) severity and improvement scales, Positive and Negative Syndrome Scale, and the Calgary Depression Scale for Schizophrenia. At study end, there were no significant differences on any rating scale between improvements in the olanzapine group and those in the ziprasidone group. At endpoint, 36.8% of the olanzapine group and 48.5% of the ziprasidone group had discontinued. Overall, 39.8% and 46.3% of the olanzapine and ziprasidone groups, respectively, had experienced adverse events that were considered treatment related. No between-group differences were seen related to dyskinesia, dystonia, or extrapyramidal symptoms. Weight gain amounted to approximately 3.5 kilograms (kg) and 1 kg for olanzapine- and ziprasidone-treated patients, respectively (p less than 0.0001). Total cholesterol, low- density lipoprotein cholesterol, and triglycerides increased by approximately 10%, 13%, and 25%, respectively, in the group receiving olanzapine; all the same measures decreased slightly in the ziprasidone group (p less than 0.0001; p=0.0004; p less than 0.003, respectively). Fasting serum insulin increased by median 3.3 and 0.25 micro- units/milliliter in the olanzapine and ziprasidone groups, respectively (p=0.051). Prolongation of the QTc interval amounted to 0.52 and 6.08 milliseconds for the same 2 groups, respectively (p less than 0.05) (Simpson et al, 2004).

**b)** A multicenter, randomized, double-blind, parallel-group, 28 week study (n=548) found that olanzapine therapy resulted in significantly greater psychopathology improvement and higher response and completion rates compared to ziprasidone, while ziprasidone therapy was superior for weight change and lipid profile. Patients with schizophrenia were randomized to receive olanzapine (n=277) 10 to 20 mg/day or ziprasidone (n=271) 80 to 160 mg/day. The primary efficacy measure, the Positive and Negative Syndrome Scale total score, showed that the olanzapine group had significantly greater improvement than the ziprasidone group (p less than 0.001). The olanzapine group also showed significant improvement from baseline to endpoint compared to ziprasidone in the Positive and Negative Syndrome subscales: positive symptoms, negative symptoms, general psychopathology, cognition, and excitability (all p less than 0.0001 except for negative symptoms p=0.003). Patients were allowed to take benzodiazepines or hypnotic monotherapy during the study, but were removed from the study if they required more than two concurrent benzodiazepine hypnotic medications. Significantly more patients in the ziprasidone group required at least one dose of a benzodiazepine compared to the olanzapine group (53.5% versus 40.4%; p=0.003). Response was defined as a 30% improvement in the Positive and Negative Syndrome Scale total score at endpoint, and the rate was significantly higher for the olanzapine group compared to the ziprasidone group (58.6% versus 42.5%) (p less than 0.001). There was no significant difference in exacerbation of symptoms between the two groups, which was defined as a decrease in the Positive and Negative Syndrome Scale total score by 20% or more and a decrease in the Clinical Global Impression severity of illness score of 1 point or more after week 8 (14.6% olanzapine and 25.3% ziprasidone; p=0.06). Significantly more patients in the olanzapine group (59.6%) than in the ziprasidone group (42.4%) completed the study (p less than 0.001). Reasons for discontinuation were only significant for lack of efficacy (olanzapine 7.2% versus ziprasidone 13.7%; p=0.02) and aggravation of psychosis (olanzapine 1.4% versus ziprasidone 4.4%; p=0.05). There were significantly greater increases in body weight and levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides (all p less than 0.001) and a significantly greater decrease in high-density lipoprotein cholesterol (p=0.001) in the olanzapine group than in the ziprasidone group (Breier et al, 2005).

**6.0 References**

AMA Department of DrugsAMA Department of Drugs: Drug Evaluations Subscription, American Medical Association, Chicago, IL, 1994.

Aarsland D, Larsen JP, Lim NG, et al: Olanzapine for psychosis in patients with Parkinson's disease with and without dementia. J Neuropsychiatry Clin Neurosci 1999; 11(3):392-394.

Abramson LB, Brown AJ, & Sitaram N: A cardioacceleratory response to low-dose arecoline infusion during sleep in patients with major depressive disorder: relationship to REM sleep induction. Psych Res 1985; 16:189-198.

Adam BS & Kashani JH: Trichotillomania in children and adolescents: review of the literature and case report. Child Psychiatry Hum Dev 1990; 20(3):159-168.

Adams BB & Mutasim DF: Pustular eruption induced by olanzapine, a novel antipsychotic agent. J Am Acad Dermatol 1999; 41:851-853.

Addonizio G, Roth SD, Stokes PE, et al: Increased extrapyramidal symptoms with addition of lithium to neuroleptics. J Nerv Ment Dis 1988; 176:682-685.

Addonizio G, Roth SD, Stokes PE, et al: Increased extrapyramidal symptoms with addition of lithium to neuroleptics. J Nerv Ment Dis 1988a; 176:682-685.

Almeida OP: Olanzapine for the treatment of tardive dyskinesia (letter). J Clin Psychiatry 1998; 49:380-381,.

Almond S & O'Donnell: Cost analysis of the treatment of schizophrenia in the UK: a comparison of olanzapine and haloperidol. Pharmacoeconomics 1998; 13:575-588.

Altshuler L, Cohen L, Szuba M, et al: Pharmacologic management of psychiatric illness during pregnancy: Dilemmas and guidelines. Am J Psychiatry 1996; 153:592-606.

Amdisen A: Lithium and drug interactions. Drugs 1982; 24:133-139.

Ananth J & Kenan J: Tardive dyskinesia associated with olanzapine monotherapy (letter). J Clin Psychiatry 1999; 60(12):870.

Angus S, Sugars J, Boltezar R, et al: A controlled trial of amantadine hydrochloride and neuroleptics in the treatment o f tardive dyskinesia. J Clin Psychopharmacol 1997; 17(2):88-91.

Anon: Drugs & Therapy Perspectives. November 28 1994; 4:7-8.

Anon: Drugs & Therapy Perspectives. November 28 1994a; 4:7-8.

Anon: Drugs & Therapy Perspectives. November 28 1994b; 4:7-8.

Anon: F-D-C Reports: The Pink Sheet. ; T&G 10, December 18, 1995a.

連

Anon: F-D-C Reports: The Pink Sheet. ; T&G 10, December 18, 1995b.

Anon: F-D-C Reports: The Pink Sheet. ; T&G#10, December 18, 1995.

Anon: FDA Talk Paper: FDA Issues Public Health Advisory for Antipsychotic Drugs used for Treatment of Behavioral Disorders in Elderly Patients. April 11, 2005.. Available at: http://www.fda.gov/bbs/topics/ANSWERSANS01350.html (cited 04/15/2005)., /2005/.

Anon: FDA approved zyprexa (olanzapine) for long-term treatment of schizophrenia.. Available at: http://www.docguide.com/news/content.nsf/Ne.../DA2A364C005BC53D852569960050F3E, November 13, 2000.

Anon: Inpharma Weekly, 953, Adis International Ltd, Auckland, New Zealand, 1994aa, pp 8-9.

Anon: Practice guideline for the treatment of patients with schizophrenia. Am J Psychiatry 1997; 154(suppl):1-63.

Anon: SCRIP World Pharmaceutical News. PJB Publications Ltd, London, UK; No 2093, p 27, January 12, 1996.

AnonAnon: Inpharma Weekly, 953, Adis International Ltd, Auckland, New Zealand, 1994a, pp 8-9.

Apple JE & Van Hauer G: Neuroleptic malignant syndrome associated with olanzapine therapy. Psychosomatics 1999; 40(3):267-268.

Arranz J & Ganoza C: Treatment of chronic dyskinesia with CDP-choline. Arzneimittelforschung 1983; 33:1071-1073.

Ashton AK: Olanzapine augmentation for trichotillomania (letter). Am J Psychiatry 2001; 158(11):1929-1930.

Baker RW, Kinon BJ, Maguire GA, et al: Effectiveness of rapid dose escalation of up to forty milligrams per day of oral olanzapine in acute agitation. J Clin Psychopharmacol 2003; 23(4):342-348.

Barbui C: Olanzapine on trial (letter). Am J Psychiatry 1998; 155:153.

Barcai A: Acta Psychiatr Scand 1977; 55:97-101. Acta Psychiatr Scand 1977; 55:97-101.

Bassitt DP & Neto MRL: Clozapine efficacy in tardive dyskinesia in schizophrenic patients. Eur Arch Psychiatry Clin Neurosci 1998; 248:209-211.

Batagol RBatagol R (Ed): Australian Drug Evaluation Committee: Medicines in Pregnancy-An Australian categorisation of risk of drug use in pregnancy, 3rd. Australian Government Publishing Service, Canberra, Australia, 1996.

Beasley CM Jr, Sanger T, Satterlee W, et al: Olanzapine versus placebo: results of a double-blind, fixed-dose olanzapine trial. Psychopharmacology 1996a; 124:159-167.

Beasley CM Jr, Sanger T, Satterlee W, et al: Olanzapine versus placebo: results of a double-blind, fixed-dose olanzapine trial. Psychopharmacology 1996aa; 124:159-167.

Beasley CM Jr, Tollefson G, & Tran P: Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacology 1996; 14:111-123.

Beasley CM, Tollefson DG & Tran PV: Efficacy of olanzapine: an overview of pivotal clinical trials. J Clin Psychiatry; 58(suppl 10)7-12, 1997.

Beasley CM, Tollefson DG & Tran PV: Efficacy of olanzapine: an overview of pivotal clinical trials. J Clin Psychiatry; 58(suppl 10)7-12, 1997a.

Beasley CM, Tollefson GD, & Tran PV: Safety of olanzapine. J Clin Psychiatry 1997a; 58(suppl 10):13-17.

Benedetti F, Cavallaro R, & Smeraldi E: Olanzapine-induced neutropenia after clozapine-induced neutropenia (letter). Lancet 1999; 354:567.

Berk M, Brook k S, & Trandafir AI: A comparison of olanzapine with haloperidol in cannabis-induced psychotic disorder: a double-blind randomized controlled trial. Int Clin Psychopharmacol 1999; 14:177-180.

Berk M, Ichim L, & Brook S: Olanzapine compared to lithium in mania: a double-blind randomized controlled trial. Int Clin Psychopharmacol 1999a; 14:339-343.

Bever KA & Perry PJ: Olanzapine: a serotonin-dopamine-receptor antagonist for antipsychotic therapy. Am J Health Syst Pharm 1998; 55:1003-1016.

Bever KA & Perry PJ: Olanzapine: a serotonin-dopamine-receptor antagonist for antipsychotic therapy. Am J Health Syst Pharm 1998a; 55:1003-1016.

Bhandary AN & Masand PS: Buspirone in the management of disruptive behaviors due to Huntington's disease and other neurological disorders. Psychosomatics 1997; 38:389-391.

Bilder RM, Goldman RS, Volavka J, et al: Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. Am J Psychiatry 2002; 159(6):1018-1028.

Bilder RM, Goldman RS, Volavka J, et al: Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. Am J Psychiatry 2002a; 159(6):1018-1028.

Bilder RM, Goldman RS, Volavka J, et al: Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. Am J Psychiatry 2002b; 159(6):1018-1028.

Blake LM, Marks RC, & Luchins DJ: Reversible neurologic symptoms with clozapine and lithium. J Clin Psychopharmacol 1992; 12:297-299.

Block C, West SA, & Baharoglu B: Paroxetine treatment of trichotillomania in an adolescent. J Child Adolesc Psychopharmacol 1998; 8(1):69-71.

Blumenthal, M, Busse WR, et alBlumenthal, M, Busse WR, et al (Eds): The Complete German Commission E Monographs, 1st. American Botanical Council, Austin, TX, 1998, pp 87-88.

Boachie A, Goldfield GS, & Spettigue W: Olanzapine use as an adjunctive treatment for hospitalized children with anorexia nervosa: case reports. Int J Eat Disord 2003; 33:98-103.

Bogelman G, Hirschmann S, & Modai: Olanzapine and Huntington's Disease. J Clin Psychopharmacol 2001; 21(1):245.

Bonelli RM, Niederwieser G, Tribl GG, et al: High-dose olanzapine in Huntington's disease. Int Clin Psychopharmacol 2002; 17(2):91-93.

Bouwer C & Stein DJ: Trichobezoars in trichotillomania: case report and literature overview. Psychosom Med 1998; 60(5):658-660.

Breier A, Berg PH, Thakore JH, et al: Olanzapine versus ziprasidone: results of a 28-week double-blind study in patients with schizophrenia. Am J Psychiatry 2005; 162:1879-1887.

Breitbart W, Tremblay A, & Gibson C: An open trial of olanzapine for the treatment of delirium in hospitalized cancer patients. Psychosomatics 2002; 43(3):175-182.

Bronson BD & Lindenmayer JP: Adverse effects of high-dose olanzapine in treatment-refractory schizophrenia (letter). J Clin Psychopharmacol 2000; 20:382-384.

Brown CS, Markowitz JS, Moore TR, et al: Atypical antipsychotics: part II adverse effects, drug interations, and costs. Ann Pharmacotherap 1999; 33:210.

Buist, A: Treating mental illness in lactating women. Medscape Women's Health 2001; 6(2); electronic version, 2001.

Capehart BP & Holsinger T: Olanzapine on trial (letter). Am J Psychiatry 1998; 155:152.

Carli M, Anand-Srivastava MB, Molina-Holgado E, et al: Effects of chronic lithium treatments on central dopaminergic receptor systems: G proteins as possible targets. Neurochem Int 1994; 24:13-22.

Carlson CD, Cavazzoni PA, Berg PH, et al: An integrated analysis of acute treatment-emergent extrapyramidal syndrome in patients with schizophrenia during olanzapine clinical trials: comparisons with placebo, haloperidol, risperidone, or clozapine. J Clin Psychiatry 2003; 64(8):898-906.

Carlson CD, Cavazzoni PA, Berg PH, et al: An integrated analysis of acute treatment-emergent extrapyramidal syndrome in patients with schizophrenia during olanzapine clinical trials: comparisons with placebo, haloperidol, risperidone, or clozapine. J Clin Psychiatry 2003a; 64(8):898-906.

Carlson CD, Cavazzoni PA, Berg PH, et al: An integrated analysis of acute treatment-emergent extrapyramidal syndrome in patients with schizophrenia during olanzapine clinical trials: comparisons with placebo, haloperidol, risperidone, or clozapine. J Clin Psychiatry 2003b; 64(8):898-906.

Cassano GB, Miniati M, Pini S, et al: Six-month open trial of haloperidol as an adjunctive treatment for anorexia nervosa: a preliminary report. Int J Eat Disord 2003; 33:172-177.

Chan Y-C, Pariser SF, & Neufeld G: Atypical antipsychotics in older adults. Pharmacotherapy 1999; 19(7):811-822.

Chen B & Cardasis W: Delirium induced by lithium and risperidone combination (letter). Am J Psychiatry 1996; 153:1233-1234.

Chengappa KN, Pollock BG, Parepally H, et al: Anticholinergic differences among patients receiving standard clinical doses of olanzapine or clozapine. J Clin Psychopharmacol 2000; 20(3):311-6.

Childers RT Jr: Report of two cases of trichotillomania of long standing duration and their response to chlorpromazine. J Clin Psychopath 1958; 19:141-144.

Christenson GA, Popkin MK, Mackenzie TB, et al: Lithium treatment of chronic hair pulling. J Clin Psychiatry 1991c; 52(3):116-120.

Christenson GA, Pyle RL, & Mitchell JE: Estimated lifetime prevalence of trichotillomania in college students. J Clin Psychiatry 1991a; 2(10):415-417.

Chu NS: Sympathetic response to betel chewing. J Psychoact Drugs 1995; 27(2):183-186.

Citrome L, Volavka J, Czobor P, et al: Effects of clozapine, olanzapine, risperidone, and haloperidol on hostility among patients with schizophrenia. Psych Serv 2001; 52(11):1510-1514.

Class CA, Schneider L, & Farlow MR: Optimal management of behavioural disorders associated with dementia. Drugs Aging 1997; 10(2):95-106.

Cohen LG, Fatalo A, Thompson BT, et al: Olanzapine overdose with serum concentrations. Ann Emerg Med 1999; 34:275-278.

Cohen WJ & Cohen NH: Lithium carbonate, haloperidol and irreversible brain damage. JAMA 1974; 230:1283-1287.

Colenda CC: Buspirone in treatment of agitated demented patient. Lancet 1988; 1:1169.

Conley RR & Meltzer HY: Adverse events related to olanzapine. J Clin Psychiatry 2000; 61(8):26-29.

Conley RR, Tamminga CA, Bartko JJ, et al: Olanzapine compared with chlorpromazine in treatment-resistant schizophrenia. Am J Psychiatry 1998; 155:914-920.

Crisp AH, Lacey JH, & Crutchfield M: Clomipramine and "drive" in people with anorexia nervosa: an in-patient study. Br J Psychiatry 1987; 150:355-358.

Croke S, Buist A, Hackett LP, et al: Olanzapine excretion in human breast milk: estimation of infant exposure. Intl J Neuropsychopharmacol 2002; 5:243-247.

Cummings JL, Street J, Masterman D, et al: Efficacy of olanzapine in the treatment of psychosis in dementia with Lewy bodies. Dement Geriatr Cogn Disord 2002; 13(2):67-73.

Czekalla J, Kollack-Walker S, Beasley CM, et al: Cardiac safety parameters of olanzapine: comparison with other atypical and typical antipsychotics. J Clin Psychiatry 2001; 62(Suppl 2):35-40.

Deahl M: Betel nut-induced extrapyramidal syndrome: an unusual drug interaction. Movement Disord 1989; 4(4):330-333.

Deahl M: Betel nut-induced extrapyramidal syndrome: an unusual drug interaction. Movement Disord 1989a; 4(4):330-333.

Deirmenjian JM, Erhart SM, Wirshing DA, et al: Olanzapine-induced reversible priapism: a case report (letter). J Clin Psychopharmacol 1998; 18(4):351-353.

DelBello MP, Foster KD, & Strakowski SM: Case report: treatment of catatonia in an adolescent male. J Adolesc Health 2000; 27:69-71.

Dellva MA & Tran Tollefson GD: Standard olanzapine versus placebo and ineffective-dose olanzapine in the maintenance treatment of schizophreinia. Psychiatr Serv 1997; 48:1571-1577.

Demb HB & Roychoudhury K: Comments on "onlanzapine treatment of children, adolescents, and adults with pervasive developmental disorders: an open-label pilot study.". J Clin Psychopharmacol 2000; 20(5):580-581.

Deshauer D, Albuquerque J, Alda M, et al: Seizures caused by possible interaction between olanzapine and clomipramine. J Clin Psychopharmacol 2000; 20(2):283-284.

Deshauer D, Albuquerque J, Alda M, et al: Seizures caused by possible interaction between olanzapine and clomipramine. J Clin Psychopharmacol 2000a; 20 (2):283-284.

Devanand DP, Sackeim HA, Brown RP, et al: A pilot study of haloperidol treatment of psychosis and behavioral disturbance in Alzheimer's disease. Arch Neurol 1989; 46:854-857.

Dickson RA & Dawson DT: Olanzapine and pregnancy (letter). Can J Psychiatry 1998; 43(2):196-197.

Dinakar HS, Sobel RN, Bopp JH, et al: Efficacy of olanzapine and risperidone for treatment- refractory schizophrenia among long-stay state hospital patients. Psychiatr Serv 2002; 53(6):755-757.

Dipple HC: The use of olanzapine for movement disorder in Huntington's disease: a first case report (letter). J Neurol Neurosurg Psychiat 1999; 67(1):123-124.

Doucette DE, Grenier JPMS, & Robertson PS: Olanzapine-induced acute pancreatitis. Ann Pharmacother 2000; 34:1128-1131.

Dunayevich E & Strakowski SM: Olanzapine-induced tardive dystonia (letter). Am J Psychiatry 1999; 156:1662.

Duncan E, Adler L, Angrist B, et al: Nifedipine in the treatment of tardive dyskinesia. J Clin Psychopharmacol 1990; 10:413-416.

Edgell ET, Anderson SW, Johnstone BM, et al: Olanzapine versus risperidone. A prospective comparison of clinical and economic outcomes in schizophrenia. Pharmacoeconomics 2000; 18:567-579.

Egan MF, Hyde TM, Albers GW, et al: Treatment of tardive dyskinesia with vitamin E. Am J Psychiatry 1992; 149:773-777.

Elkashef AM, Ruskin PE, Bacher N, et al: Vitamin E in the treatment of tardive dyskinesia. Am J Psychiatry 1990; 147:505-506.

Epperson CN, Fasula D, Wasylink S, et al: Risperidone addition in serotonin reuptake inhibitors resistant

trichotillomania: three cases. J Child Adolesc Psychopharmacol 1999; 9(1):43-49.

Epperson NC, McDougle CJ, & Price LH: Intranasal oxytocin in trichotillomania. Biol Psychiatry 1996; 40:559-560.

Ernst CL & Goldberg JF: The reproductive safety profile of mood stabilizers, atypical antipsychotics, and broad-spectrum psychotropics. J Clin Psychiatry 2002; 63(suppl 4):42-55.

Falsetti AE: Olanazpine: psychopharmacology, clinical efficacy, and adverse effects. Hosp Pharm 1999; 34:423-435.

Fanous A & Lindenmayer J-P: Schizophrenia and schizoaffective disorder treated with high doses of olanzapine. J Cllin Psychopharmacol 1999; 19(3):275-276.

Filice GA, McDougall BC, Ercan-Fang N, et al: Neuroleptic malignant syndrome associated with olanzapine. Ann Pharmacother 1998; 32:1158-1159.

Foti ME & Pies RW: Lithium carbonate and tardive dyskinesia (letter). J Clin Psychopharmacol 1986; 6:325.

Frazier JA, Biederman J, Tohen M, et al: A prospective open-label treatment trial of olanzapine monotherapy in children and adolescents with bipolar disorder. J Child Adolesc Psychopharmacol 2001; 11(3):239-250.

Friedman A & Sienkiewicz J: Psychotic complications of long-term levodopa treatment of Parkinson's disease. Act Neurol Scand 1991; 84:111-113.

Friedman JH & Factor SA: Atypical antipsychotics in the treatment of drug-induced psychosis in Parkinson's disease. Mov Disord 2000; 15(2):201-211.

Friedman JH, Max J, & Swift R: Idiopathic parkinson's disease in a chronic schizophrenic patient: long-term treatment with clozapine and l-dopa. Clin Neuropharmacol 1987; 10:470-475.

Friedman JH: Clozapine treatment of psychosis in patients with tardive dystonia: report of three cases. Mov Disord 1994; 9:321-324.

Friedman JH: Review: the management of the levodopa psychoses. Clin Neuropharmacology 1991; 14:283-295.

Fukunishi I, Sato Y, Kino K, et al: Hypothermia in a hemodialysis patient treated with olanzapine monotherapy. J Clin Psychopharmacol 2003; 21:113-115.

Fuller RW & Snoddy HD: Neuroendocrine evidence for antagonism of serotonin and dopamine receptors by olanzapine (LY170053), an antipsychotic drug candidate. Res Comm Chemical Pathology Pharmacology 1992; 77:87-93.

Fulton B & Goa KL: Olanzapine. A review of its pharmacological properties and therapeutic efficacy in the management of schizophrenia and related psychoses. Drugs 1997; 53:281-298.

Gardiner SJ, Kristensen JH, Begg EJ, et al: Transfer of olanzapine into breast milk, calculation of infant drug dose, and effect on breast-fed infants. Am J Psychiatry 2003; 160(8):1428-1431.

Gardos G, Cole JO, Matthews JD, et al: The acute effects of a loading dose of phenylalanine in unipolar depressed

patients with and without tardive dyskinesia. Neuropsychopharmacology 1992; 6(4):241-247.

Gardos G, Cole JO, Matthews JD, et al: The acute effects of a loading dose of phenylalanine in unipolar depressed patients with and without tardive dyskinesia. Neuropsychopharmacology 1992a; 6(4):241-247.

Gatta B, Rigalleau V, & Gin H+: Diabetic ketoacidosis with olanzapine treatment. Diabetes Care 1999; 22:1002-1003.

Gelenberg AJ, Dorer DJ, Wojcik JD, et al: A crossover study of lecithin treatment of tardive dyskinesia. J Clin Psychiatry 1990; 51:149-153.

Gelenberg AJ, Wojcik J, Falk WE, et al: CDP-choline for the treatment of tardive dyskinesia: a small negative series. Compr Psychiatry 1989; 30:1-4.

Gheorghiu S, Knobler HY, & Drumer D: Recurrence of neuroleptic malignant syndrome with olanzapine treatment (letter). Am J Psychiatry 1999; 156(11):1836.

Gheuens J & Grebb JA: Comments on article by Tran and colleagues, "double-blind comparison of olanzapine versus risperidone in treatment of schizophrenia and other psychotic disorders" (letter). J Clin Psychopharmacol 1998; 18(2):176-177.

Gimenez-Roldan S & Mateo D Navarro E: Efficacy and safety of clozapine and olanzapine: an open label study comparing two groups of Parkinson's disease patients with dopaminergic-induced psychosis. Parkinsonism Rel Disord 2001; 7:121-127.

Glazer WM: Extrapyramidal side effects, Tardive dyskinesia, and the concept of atypicality. J Clin Psychiatry 2000; 61(suppl 3):16-21.

Glazer WM: Extrapyramidal side effects, Tardive dyskinesia, and the concept of atypicality. J Clin Psychiatry 2000a; 61(suppl 3):16-21.

Gleason RP & Schneider LS: Carbamazepine treatment of agitation in alzheimer's outpatients refractory to neuroleptics. J Clin Psychiatry 1990; 51:115-118.

Goldenberg G, Kahaner K, Basavaraju N, et al: Gabapentin for disruptive behaviors in an elderly demented patient. Drugs Aging 1998; 13(2):183-184.

Goldney RD & Spence ND: Safety of the combination of lithium and neuroleptic drugs. Am J Psychiatry 1986; 143:882-884.

Goldstein D, Corbin L, & Fung M: Olanzapine-exposed pregnancies and lactation: early experience. J Clin Psychopharmacol 2000a; 20(4):399-403.

Goldstein DJ, Corbin LA, & Fung MC: Olanzapine-exposed pregnancies and lactation: Early experience. J Clin Psychopharmacol 2000; 20:399-403.

Goldstein LE, Sporn J, & Brown S: New-onset diabetes mellitus and diabetic ketoacidosis associated with olanzapine treatment. Psychosomatics 1999; 40(5):438-443.

Gomberg RF: Interaction between olanzapine and haloperidol (letter). J Clin Psychopharmacol 1999; 19:272-273.

Gomberg RF: Interaction between olanzapine and haloperidol (letter). J Clin Psychopharmacol 1999a; 19:272-273.

Gomez JC, Sacristan JA, Hernandex J, et al: The safety of olanzapine compared with other antipsychotic drugs: results of an observational prospective study in patients with schizophrenia (EFESO study). J Clin Psychiatry 2000; 61(5):335-343.

Goodwin FK: Psychiatric side effects of levodopa in man. JAMA 1971; 218:1915-1920.

Gordon M & De Groot CM: Olanzapine-associated priapism (letter). J Clin Psychopharmacol 1999; 19(2):192.

Graae F, Gitow A, Piacentini J, et al: Response of obsessive-compulsive disorder and trichotillomania to serotonin reuptake blockers. Am J Psychiatry 1992; 149(1):149-150.

Graham JM, Sussman JD, Ford KS, et al: Olanzapine in the treatment of hallucinosis in idiopathic parkinson's disease: a cautionary note. J Neurol Neurosurg Psychiatry 1998a; 65:774-777.

Graham JM, Sussman JD, Ford KS, et al: Olanzapine in the treatment of hallucinosis in idiopathic parkinson's disease: a cautionary note. J Neurol Neurosurg Psychiatry 1998; 65:774-777.

Granger AS & Hanger HC: Olanzapine: extrapyramidal side effects in the elderly (letter). Aust N Z J Med 1999; 29:371-372.

Gross HA: J Clin Psychopharmacol 1981; 1:376-381. J Clin Psychopharmacol 1981; 1:376-381.

Grossman F: A review of anticonvulsants in treating agitated demented elderly patients. Pharmacotherapy 1998; 18(3):600-606.

Grothe DR, Calis KA, Jacobsen L, et al: Olanzapine pharmacokinetics in pediatric and adolescent inpatients with childhood-onset schizophrenia. J Clin Psychopharmacol 2000; 20(2):220-225.

Grove VE, Quintanilla J, & DeVaney GT: Improvement of Huntington's disease with olanzapine and valproate. N Engl J Med 2000; 343(13):973-974.

Guille C, Sachs GS, & Ghaemi SN: A naturalistic comparison of clozapine, risperidone, and olanzapine in the treatment of bipolar disorder. J Clin Psychiatry 2000; 61(9):638-642.

Guille C, Sachs GS, & Ghaemi SN: A naturalistic comparison of clozapine, risperidone, and olanzapine in the treatment of bipolar disorder. J Clin Psychiatry 2000a; 61(9):638-642.

Gupta MA & Gupta AK: Olanzapine is effective in the management of some self-induced dermatoses: three case reports. Cutis 2000; 66:143-146.

Gupta S, Droney T, Al-Samarrai S, et al: Olanzapine: weight gain and therapeutic efficacy (letter). J Clin Psychopharmacol 1999; 19(3):273-275.

Halmi KA, Eckert E & Falk JR: Cyproheptadine, an antidepressant and weight-inducing drug for anorexia nervosa. Psychopharmacol Bull; 19:103-105. 8. Halmi, 1983.

Hansen L: Olanzapine in the treatment of anorexia nervosa (letter). Br J Psychiatry 1999; 175:592.

Harvey AM, Johns RJ, McKusick VA, et al (Eds): The Principles and Practice of Medicine, Appleton & Lange, Norwalk, CT, 1988.

Harvey EJ, Flanagan RJ, & Taylor DM: The preparation and stability of a liquid olanzapine preparation for oral administration in hospitals. Pharm J 2000; 265:275-276.

Heckers S, Anick D, Boverman JF, et al: Priapism following olanzapine administration in a patient with multiple sclerosis. Psychomatics 1998; 39:288-290.

Herran A & Vazquez-Barquero JL: Tardive dyskinesia associated with olanzapine (letter). Ann Intern Med 1999; 131(1):72.

Herrmann N, Lanctot K, & Myszak M: Effectiveness of gabapentin for the treatment of behavioral disorders in dementia. J Clin Psychopharmacol 2000; 20(1):90-93.

Herrmann N, Rivard M-F, Flynn M, et al: Risperidone for the treatment of behavioral disturbances in dementia: a case series. J Neuropsychiatr Clin Neurosci 1998; 10:220-223.

Herrmann N: Valproic acid treatment of agitation in dementia. Can J Psychiatry 1998; 43:69-72.

Hiemke C, Peled A, Jabarin M, et al: Fluvoxamine augmentation of olanzapine in chronic schizophrenia: pharmacokinetic interactions and clinical effects. J Clin Psychopharmacol 2002; 22(5):502-506.

Higgins G: Risperidone: will it significantly change schizophrenia therapy?. Inpharma 1993; 892:5-6.

Hirschfeld R, Baker J, Wozniak P, et al: The safety and early efficacy of oral-loaded divalproex versus standard-titration divalproex, lithium, olanzapine, and placebo in the treatment of acute mania associated with bipolar disorder. J Clin Psychiatry 2003; 64:841-846.

Hirschfeld R, Baker J, Wozniak P, et al: The safety and early efficacy of oral-loaded divalproex versus standard-titration divalproex, lithium, olanzapine, and placebo in the treatment of acute mania associated with bipolar disorder. J Clin Psychiatry 2003a; 64:841-846.

Ho BC, Miller D, Nopoulos P, et al: A comparative effectiveness study of risperidone and olanzapine in the treatment of schizophrenia. J Clin Psychiatry 1999; 60(10):658-663.

Hoffman L & Halmi K: Psychopharmacology in the treatment of anorexia nervosa and bulimia nervosa. Psychiatr Clin North Am 1993; 16:767-778.

Howard JE: Severe psychosis and the adrenal androgens. Integr Physiol Behav Sci 1992; 27:209-215.

Howard JE: Severe psychosis and the adrenal androgens. Integr Physiol Behav Sci 1992a; 27:209-215.

Iancu I, Weizman A, & Kindler S: Serotonergic drugs in trichotillomania: treatment results in 12 patients. J Nerv Ment Dis 1996; 184(10):641-644.

Irizarry MC, Ghaemi SN, Lee-Cherry ER, et al: Risperidone treatment of behavioral disturbances in outpatients with dementia. J Neuropsychiatry Clin Neurosci 1999; 11(3):336-342.

Isbister GK, Whyte IM, & Smith AJ: Olanzapine overdose (letter). Anaesthesia 2001; 56:400-401.

Ishigooka J, Inada T, & Miura S: Olanzapine versus haloperidol in the treatment of patients with chronic schizophrenia: results of the Japan multicenter, double-blind olanzapine trial. Psychiatry Clin Neurosci 2001; 55:403-414.

Ishigooka J, Murasaki M, Miura S, et al: Efficacy and safety of olanzapine, an atypical antipsychotic, in patiens with schizophrenia: results of an open-label multicenter study in Japan. Psychiatry Clin Neurosci 2001a; 55:353-363.

Janowsky DS, El-Yousef MK, Davis JM, et al: Effects of amantadine on tardive dyskinesia and pseudo-Parkinsonism. N Engl J Med 1972; 286:785.

Jefferys D: Trichotillomania - an overview. Exp Dermatol 1999; 8(4):298-299.

Jeshi AA: Paranoia and agitation associated with olanzapine treatment (letter). Can J Psychiatry 1998; 43(2):195-196.

Jeste DV, Barak Y, Madhusoodanan S, et al: International multisite double-blind trial of the atypical antipsychotics risperidone and olanzapine in 175 elderly patients with chronic schizophrenia. Am J Geriatr Psychiatry 2003; 11(6):638-647.

Jeste DV, Barak Y, Madhusoodanan S, et al: International multisite double-blind trial of the atypical antipsychotics risperidone and olanzapine in 175 elderly patients with chronic schizophrenia. Am J Geriatr Psychiatry 2003a; 11(6):638-647.

Jimenez-Jimenez FJ, Tallon-Barranco A, Orti-Pareja M, et al: Olanzapine can worsen parkinsonism. Neurology 1998; 50:1183-1184.

Johanson AJ & Knorr NJ: L-Dopa as treatment for anorexia nervosa In: Vigersky RA (Ed): Anorexia Nervosa, Raven Press, New York, NY, 1977, pp 363-372.

John V, Rapp M, & Pies R: Aggression, agitation, and mania with olanzapine. (letter). Can J Psychiatry 1998; 43(10):1054.

Jones B, Taylor CC, & Meehan K: The efficacy of a rapid-acting intramuscular formulation of olanzapine for positive symptoms. J Clin Psych 2000; 62(suppl 2):22-24.

Juncos JL: Management of psychotic aspects of Parkinson's disease. J Clin Psychiatry 1999; 60((suppl 8)):42-53.

Kahn N, Freeman A, Juncos JL et al: Clozapine is beneficial for psychosis in Parkinson's disease. Neurology 1991; 1699-1700, 1991.

Kampman KM, Pettinati H, & Lynch KG: A pilot trial of olanzapine for the treatment of cocaine dependence. Drug Alcohol Depend 2003; 70(3):265- 273.

Kando JC, Shepski J, Satterlee W, et al: Olanzapine: a new antipsychotic agent with efficacy in the management of schizophrenia. Ann Pharmacother 1997; 31:1325-1334.

Kando JC, Shepski J, Satterlee W, et al: Olanzapine: a new antipsychotic agent with efficacy in the management of schizophrenia. Ann Pharmacother 1997a; 31:1325-1334.

Kapur S, Zipursky RB, Remington G, et al: 5-HT2 and D2 receptor occupancy of olanzapine in schizophrenia: a PET investigation. Am J Psychiatry 1998; 155:921-928.

Kasckow JW, Mcelroy SL, Cameron EL, et al: A pilot study on the use of divalproex sodium in the treatment of behavioral agitation in elderly patients with dementia: assessment with the behave-ad and CGI rating scales. Curr Ther Res 1997; 58:981-989.

Kaye WH, Weltzin TE, Hsu LK, et al: An open trial of fluoxetine in patients with anorexia nervosa. J Clin Psychiatry 1991; 52:464-471.

Keck PE Jr, Strakowski SM, & McElroy SL: The efficacy of atypical antipsychotics in the treatment of depressive symptoms, hostility, and suicidality in patients with schizophrenia. J Clin Psychiatry 2000; 61(suppl 3):4-9.

Keck PE Jr, Strakowski SM, & McElroy SL: The efficacy of atypical antipsychotics in the treatment of depressive symptoms, hostility, and suicidality in patients with schizophrenia. J Clin Psychiatry 2000a; 61(suppl 3):4-9.

Keitner GI & Rahman S: Reversible neurotoxicity with combined lithium-haloperidol administration. J Clin Psychopharmacol 1984; 4:104-105.

Kern RS, Cornblatt B, Carson WH, et al: An open-label comparison of the neurocognitive effects of aripiprazole versus olanzapine in patients with stable psychosis. Schizophr Res 2001; 49(1-2):234.

Ketter TA, Winsberg ME, DeGolia SG, et al: Rapid efficacy of olanzapine augmentation in nonpsychotic bipolar mixed states (letter). J Clin Psychiatry 1998; 59(2):83-85.

Keuthen NJ, O'Sullivan RL, & Sprich-Buckminster S: Trichotillomania: current issues in conceptualization and treatment. Psychother Psychosom 1998; 67(4-5):202-213.

Kim K, Pae C, Chae J, et al: An open pilot trial of olanzapine for delirium in the Korean population. Psychiatry Clin Neurosci 2001; 55:515-519.

Kinon BJ, Basson BR, Gilmore JA, et al: Strategies for switching from conventional antipsychotic drugs or risperidone to olanzapine. J Clin Psychiatry 2000; 61(11):833-840.

Kirchheiner J, Berghofer A, & Bolk-Weischedel D: Healthy outcome under olanzapine treatment in a pregnant women (case report). Pharmacopsychiatry 2000; 33(2):78-80.

Kirchheiner J, Berhofer A, & Bolk-Weischedel D: Healthy outcome under olanzapine treatment in a pregnant woman. Pharmacopsychiatry 2000a; 33:78-80.

Koller EA, Cross JT, Doraiswamy PM, et al: Pancreatitis associated with atypical antipsychotics: from the food and drug administration¿s medwatch surveillance system and published reports. Pharmacotherapy 2003; 23(9):1123-1130.

Koller EA, Cross JT, Doraiswamy PM, et al: Pancreatitis associated with atypical antipsychotics: from the food and drug administration¿s medwatch surveillance system and published reports. Pharmacotherapy 2003a; 23(9):1123-1130.

Koller EA, Cross JT, Doraiswamy PM, et al: Pancreatitis associated with atypical antipsychotics: from the food and drug administration¿s medwatch surveillance system and published reports. Pharmacotherapy 2003b; 23(9):1123-1130.

Koller EA, Cross JT, Doraiswamy PM, et al: Pancreatitis associated with atypical antipsychotics: from the food and drug administration¿s medwatch surveillance system and published reports. Pharmacotherapy 2003c; 23(9):1123-1130.

Konakanchi R, Grace JJ, Szarowicz R, et al: Olanzapine prolongation of granulocytopenia after clozapine discontinuation (letter). J Clin Psychopharmacol 2000; 20:703-704.

Kraemer PA: The application of habit reversal in treating trichotillomania. Psychotherapy 1999; 36(3):298-304.

Kraus T, Schuld A, & Pollmacher T: Periodic leg movements in sleep and restless legs syndrome probably caused by olanzapine (letter). J Clin Psychopharmacol 1999; 19(5):478-479.

Krishnan RR, Davidson J, & Miller R: MAO inhibitor therapy in trichotillomania associated with depression: case report. J Clin Psychiatry 1984; 45:267-268.

Kristine Healey, PharmD, Medical Information Services, Eli Lilly and Company

Kuperman JR, Asher I, & Modai I: Olanzapine-associated priapism. J Clin Psychopharmacol 2001; 21(2):247.

Landi F, Cesari M, Zuccala G, et al: Olanzapine and hypoglycemic coma in a frail elderly woman. Pharmacopsychiatry 2003; 36(4):165-166.

Landry P & Cournoyer J: Acute dystonia with olanzapine (letter). J Clin Psychiatry 1998; 59:384.

Lang AE & Lozano AM: Parkinson's disease: second of two parts. N Engl J Med 1998; 339(16):1130-1143.

Lee JW, Crismon LM, & Dorson PG: Seizure associated with olanzapine. Ann Pharmacotherap 1999; 33:554-555.

Levenson JL: Neuroleptic malignant syndrome after the initiation of olanzapine (letter). J Clin Psychopharmacol 1999; 19(5):477-478.

Lewis R: Typical and atypical antipsychotics in adolescent schizophrenia: efficacy, tolerability, and differential sensitivity to extrapyramidal symptoms. Can J Psychiatry 1998; 43:596-604.

Leys D, Vermersch P, Danel T, et al: Diltiazem for tardive dyskinesia. Lancet 1988; 1:250-251.

Licht RW, Olesen OV, Friis P, et al: Olanzapine serum concentrations lowered by concomitant treatment with carbamazepine (letter). J Clin Psychopharmacol 2000; 20:110-112.

Licht RW, Olesen OV, Friis P, et al: Olanzapine serum concentrations lowered by concomitant treatment with carbamazepine (letter). J Clin Psychopharmacol 2000a; 20:110-112.

Lieberman JA, Stroup TS, McEvoy JP, et al: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Eng J Med 2005; 353:1209-1223.

Lieberman JA, Yunis J, Egea E, et al: HLA-B38, DR4, DQw3 and clozapine-induced agranulocytosis in Jewish patients with schizophrenia. Arch Gen Psychiatry 1990; 47:945-948.

Lindenmayer J-P & Patel R: Olanzapine-induced ketoacidosis with diabetes mellitus (letter). Am J Psychiatry 1999; 156(9):1471.

Lindenmayer JP & Klebanov R: Olanzapine-induced manic-like syndrome (letter). J Clin Psychiatry 1998; 59(6):318-319.

Littrell KH, Johnson CG, Littrell S, et al: Marked reduction of tardive dyskinesia with olanzapine. Arch Gen Psychiatry 1998; 55:279-280.

Littrell KH, Johnson CG, Littrell SH, et al: Effects of olanzapine on polydipsia and intermittent hyponatremia (letter). J Clin Psychiatry 1997; 58:549.

Littrell KH, Johnson CG, Peabody CD, et al: Antipsychotics during pregnancy. Am J Psychiatry 2000; 157(8):1342.

Lohr JB & Caligiuri MP: A double-blind placebo controlled study of vitamin E treatment of tardive dyskinesia. J Clin Psychiatry 1996; 57:167-173.

Lohr JB, Cadet JL, Lohr MA, et al: Alpha-tocopherol in tardive dyskinesia. Lancet 1987; 1:213-214.

Loudon JB & Waring H: Toxic reactions to lithium and haloperidol (letter). Lancet 1976; 2:1088.

Lucas RA, Gilfillan DJ, & Bergstrom RF: A pharmacokinetic interaction between carbamazepine and olanzapine: observations on possible mechanism. Eur J Clin Pharmacol 1998; 34:639-643.

Malina A, Gaskill J, McConaha C, et al: Olanzapine treatment of anorexia nervosa: a retrospective study. Int J Eat Disord 2003; 33:234-237.

Malone RP, Sheikh R, & Zito JM: Novel antipsychotic medications in the treatment of children and adolescents. Psychiatr Serv 1999; 50(2):171.

Maloney MJ & Farrell MK: Treatment of severe weight loss in anorexia nervosa with hyperalimentation and psychotherapy. Am J Psychiatry 1980; 137:310-314.

Mandalos GE & Szarek BL: New-onset panic attacks in a patient treated with olanzapine. J Clin Psychopharmacol 1999; 19(2):191.

Marcus E-L, Vass A, & Zislin J: Marked elevation of serum creatine kinase associated with olanzapine therapy. Ann Pharmacother 1999; 33:697-700.

Margolese HC: Olanzapine-induced neuroleptic malignant syndrome with mental retardation (letter). Am J Psychiatry 1999; 156(7):1115-1116.

Markowitz JS & DeVane CL: Suspected ciprofloxacin inhibition of olanzapine resulting in increased plasma concentration (letter). J Clin Psychopharmacol 1999; 19:289-290.

Markowitz JS & DeVane CL: Suspected ciprofloxacin inhibition of olanzapine resulting in increased plasma

concentration (letter). J Clin Psychopharmacol 1999a; 19:289-290.

Markowitz JS, Brown CS, & Moore TR: Atypical antipsychotics: part I: pharmacology, pharmacokinetics, and efficacy. Ann Pharmacother 1999; 33:73-85.

Markowitz JS, DeVane CL, Boulton DW, et al: Hypotension and bradycardia in a healthy volunteer following a single 5 mg dose of olanzapine. J Clin Pharmacol 2002; 42:104-106.

Marsden CD: Problems with long-term levodopa therapy for Parkinson's disease. Clin Neuropharmacol 1994; 17(suppl 2):S32-S44.

Martin J, Gomez JC, Garcia-Bernardo E, et al: Olanzapine in treatment-refractory schizophrenia: results of an open-label study. J Clin Psychiatry 1997; 58:479-483.

Masand PS: Side effects of antipsychotics in the elderly. J Clin Psychiatry 2000; 61(8):43-49.

Mattes JA: Olanzapine on trial (letter). Am J Psychiatry 1998; 155:153.

McKenna K, Levinson AJ, Einarson A et al: Pregnancy outcome in women receiving atypical antipsychotic drugs: A prospective, multicentre, controlled study. Presented at the American Society for Clinical Pharmacology and Therapeutics Annual Meeting; Washington, DC, USA, April 2-5, 2003.

Meco G, Alessandri A, Giustini P, et al: Risperidone in levodopa-induced psychosis in advanced Parkinson's disease: an open-label, long-term study. Mov Disord 1997; 12:610-612.

Meissner W, Schmidt T, Kupsch A, et al: Reversible leucopenia related to olanzapine (letter). Mov Disord 1999; 14(5):872-873.

Meltzer HY, Alphs L, Green AI, et al: Clozapine treatment for suicidality in schizophrenia: International suicide prevention trial (InterSePT). Arch Gen Psychiatry 2003; 60(Jan):82-91.

Mendhekar DN, Lohia D, & Jiloha RC: Olanzapine-induced galactorrhea in a woman with psychotic illness. Aust N Z J Psychiatry 2004; 38(4):266.

Mendhekar DN, War L, Sharma JB, et al: Olanzapine and pregnancy (case report). Pharmacopsychiatry 2002; 35(3):122-123.

Mendis T, Barclay CL, & Mohr E: Drug-induced psychosis in Parkinson's disease. CNS Drugs 1996; 5:166-174.

Miller F & Menninger J: Correlation of neuroleptic dose and neurotoxicity in patients given lithium and a neuroleptic. Hosp Comm Psychiatr 1987; 38:1219-1221.

Mintzer J, Faison W, Street JS, et al: Olanzapine in the treatment of anxiety symptoms due to Alzheimer's disease: a post hoc analysis. Int J Geriatr Psychiatry 2001; 16:S71-S77.

Mintzer JE, Hoernig KS, & Mirski DF: Treatment of agitation in patients with dementia. Clin Geriatr Med 1998; 14(1):147-175.

Misra LK, Kofoed L, Oesterheld JR, et al: Olanzapine treatment of methamphetamine psychosis. J Clin

Psychopharmacol 2000; 20(3):393-394.

Molho ES & Factor SA: Worsening of motor features of Parkinsonism with olanzapine. Mov Disord 1999; 14(6):1014-1016.

Moltz DA & Coeytaux RR: Case report: possible neuroleptic malignant syndrome assoicated with olanzapine (letter). J Clin Psychopharmacol 1998; 18(6):485-486.

Moore DC: Amitriptyline therapy in anorexia nervosa. Am J Psychiatry 1977; 134:1303-1304.

Moore NA, Tye NC, Axton MS, et al: The behavioral pharmacology of olanzapine, a novel "atypical" antipsychotic agent. J Pharmacol Exp Ther 1992; 262:545-551.

Moore R: Naloxone in the treatment of anorexia nervosa: Effect on weight gain and lipolysis. J Royal Soc Med 1981; 74:129-131.

Morrison D, clark D, Goldfarb E, et al: Worsening of obsessive-compulsive symptoms following treatment with olanzapine (letter). Am J Psychiatry 1998; 155:855.

Nagy A, Tenyi T, Lenard K, et al: Olanzapine and pregnancy (English abstract, Hungarian article). Orv Hetil 2001; 142(3):137-138.

Nasrallah HA, Dunner FJ, Smith RE, et al: Variable clinical response to choline in tardive dyskinesia. Psychol Med 1984; 14:697-700.

Naumann R, Felber w, Heilemann H, et al: Olanzapine-induced agranulocytosis (letter). Lancet 1999; 354(9178):566-567.

Nayudu SK & Scheftner WA: Case report of withdrawal syndrome after olanzapine discontinuation (letter). J Clin Psychopharmacol 2000; 20:489-490.

Nebel A, Schneider BJ, Baker RK, et al: Potential metabolic interaction between St. John's Wort and theophylline. Ann Pharmacotherapy 1999; 33:502.

Nemeroff CB: Dosing the antipsychotic medication olanzapine. J Clin Psych 1997; 58(suppl 10):45-49.

Nemeroff CB: Dosing the antipsychotic medication olanzapine. J Clin Psych 1997a; 58(suppl 10):45-49.

Ninan PT, Knight B, Kirk L, et al: Beyond panic: medication effects in anxiety disorders. A controlled trial of venlafaxine in trichotillomania: interim phase I results. Psychopharmacol Bull 1998; 34(2):221-224.

Nutt JG, Rosin A, & Chase TN: Treatment of Huntington disease with a cholinergic agonist. Neurology 1978; 28:1061-1064.

Nutt JG, Rosin A, & Chase TN: Treatment of Huntington disease with a cholinergic agonist. Neurology 1978a; 28:1061-1064.

Nyfort-Hansen K & Alderman CP: Possible neuroleptic malignant syndrome associated with olanzapine (letter). Ann Pharmacother 2000; 34:667.

Nyth AL & Gottfries CG: The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders: a Nordic multicentre study. Br J Psychiatry 1990; 157:894-901.

Nyth AL, Gottfries CG, Lyby K, et al: A controlled multicenter clinical study of citalopram and placebo in elderly depressed patients with and without concomitant dementia. Acta Psychiatr Scand 1992; 86:138-145.

O'Sullivan RL, Keuthen, NJ, et al: Trichotillomania: behavioral symptom or clinical syndrome?. Am J Psychiatry 1997; 154(10):1442-1449.

Osser DN, Najarian DM, & Dufresne RL: Olanzapine increases weight and serum triglyceride levels. J Clin Psychiatry 1999; 60(11):767-770.

Oyewumi LK & Al-Semaan Y: Olanzapine: safe during clozapine-induced agranulocytosis (letter). J Clin Psychopharmacol 2000; 20(2):279-281.

Pacher P & Kecskemeti V: Cardiovascular side effects of new antidepressants and antipsychotics: new drugs, old concerns?. Curr Pharm Des 2004; 10(20):2463-2475.

Palmer CJ, Yates WR, & Trotter L: Childhood trichotillomania: successful treatment with fluoxetine following an SSRI failure. Psychosomatics 1999; 40(6):526-528.

Parker G: Olanzapine augmentation in the treatment of melancholia: the trajectory of improvement in rapid responders. Int Clin Psychopharmacol 2002; 17(2):87-89.

Pasion RC & Kirby SG: Trazodone for screaming (letter). Lancet 1993; 341:970.

Passik SD, Lundenberg J, Kirsh KL, et al: A pilot exploration of the antiemetic activity of olanzapine for the relief of nausea in patients with advanced cancer and pain. J Pain Symptom Manage 2002; 23(6):526-532.

Patel NC, Kistler JS, James EB, et al: A retrospective analysis of the short-term effects of olanzapine and quetiapine on weight and body mass index in children and adolescents. Pharmacotherapy 2004; 24(7):823-830.

Patton SW, Misri S, Corral MR, et al: Antipsychotic medication during pregnancy and lactation in women with schizophrenia: Evaluating the risk. Can J Psychiatry 2002; 47(10):959-965.

Pederzoli M, Girotti F, Scigliano G, et al: L-dopa-long-term treatment in Parkinson's disease: age related side effects. Neurol 1983; 33:1518-1522.

Peet M & Peters S: Drug-induced mania. Drug Safety 1995; 12:146-153.

Penzak S, Hon Y, Lawhorn W, et al: Influence of ritonavir on olanzapine pharmacokinetics in healthy volunteers. J of Clin Psychopharmacol 2002; 22(4):366-370.

Perkins DO & McClure RK: Hypersalivation coincident with olanzapine treatment. Am J Psychiatry 1998; 155:993-994.

Perry PJ, Sanger T, & Beasley C: Olanzapine plasma concentrations and clinical response in acutely III schizophrenic patients. J Clin Psychopharmacol 1997; 17:472-477.

Personal communication.. Medical Information Department, Eli Lilly and Company., 10/25/96.

Petty F, Brannan S, Casada J, et al: Olanzapine treatment for post-traumatic stress disorder: an open-label study. Int Clin Psychopharmacol 2001; 16:331-337.

Pfeiffer C & Wagner ML: Clozapine therapy of Parkinson's disease and other movement disorders. Am J Hosp Pharm 1994; 51:3047-3053.

Pfeiffer RF, Kang J, Graber B, et al: Clozapine for psychosis in Parkinson's disease. Mov Disord 1990; 5:239-242.

Pollard CA, Ibe IO, Krojanker DN, et al: Clomipramine treatment of trichotillomania: a follow-up report on four cases. J Clin Psychiatry 1991; 52(3):128-130.

Pollock BG & Mulsant BH: Behavioral disturbances of dementia. J Geriatr Psychiatry Neurol 1998; 11:206-212.

Potenza MN & McDougle CJ: Reply to comments on "olanzapine treatment of children, adolescents, and adults with pervasive developmental disorders: an open-label pilot study.". J Clin Psychopharmacol 2001; 21(2):246-247.

Potenza MN, Holmes JP, Kanes SJ, et al: Olanazpine treatment of children, adolescents, and adults with pervasive developmental disorders: an open-label pilot study. J Clin Psychopharmacol 1999; 19(1):37-44.

Potenza MN, Wasylink S, Epperson CN, et al: Olanzapine augmentation of fluoxetine in the treatment of trichotillomania.. Am J Psychiatry 1998; 155(9):1299-1300.

Powers PS, Santana CA, & Bannon YS: Olanzapine in the treatment of anorexia nervosa: an open label trial. Int J Eat Disord 2002; 32:146- 154.

Prakash R: Lithium-haloperidol combination and brain damage (letter). Lancet 1982; 1:1468-1469.

Product Information: LUNESTA(TM), eszopiclone tablets. Sepracor Inc., Marlborough, MA, USA, 2004.

Product Information: Lithium Carbonate. Roxane Laboratories Inc., Columbus, OH, 2002.

Product Information: Orlaam(R), levomethadyl. Roxane Laboratories, Inc., Columbus, OH, 2001.

Product Information: ZYPREXA(R) injection, oral disintegrating tablets, oral tablets, olanzapine injection, oral disintegrating tablets, oral tablets. Eli Lilly and Company, Indianapolis, IN, 2004.

Product Information: ZYPREXA(R), ZYPREXA ZYDIS(R), ZYPREXA IntraMuscular(R), olanzapine tablets, orally disintegrating tablets, injection. Eli Lily and Company, Indianapolis, IN, 2005.

Product Information: Zyprexa(R), Olanzapine. Eli Lilly and Company, Indianapolis, IN, 2000a.

Product Information: Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine. Eli Lilly and Company, Indianapolis, IN, 2004.

Product Information: Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine. Eli Lilly and Company, Indianapolis, IN, 2004a.

Product Information: Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine. Eli Lilly and Company, Indianapolis, IN, 2004b.

Product Information: Zyprexa(R), olanzapine tablets, orally disintegrating tablets, and intramuscular injection. Eli Lilly and Company, Indianapolis, IN, USA, 2004.

Product Information: Zyprexa(R), olanzapine. Eli LIlly and Company, Indianapolis, IN, 1999a.

Product Information: Zyprexa(R), olanzapine. Eli Lilly & Company, Indianapolis, IN, 2003.

Product Information: Zyprexa(R), olanzapine. Eli Lilly Nederland BV, Nieuwegein, 1998.

Product Information: Zyprexa(R), olanzapine. Eli Lilly Nederland BV, Nieuwegein, 1998a.

Product Information: Zyprexa(R), olanzapine. Eli Lilly and Company, Indianapolis, IN, 1999.

Product Information: Zyprexa(R), olanzapine. Eli Lilly and Company, Indianapolis, IN, 1999b.

Product Information: Zyprexa(R), olanzapine. Eli Lilly and Company, Indianapolis, IN, 1999c.

Product Information: Zyprexa(R), olanzapine. Eli Lilly and Company, Indianapolis, IN, 1999d.

Product Information: Zyprexa(R), olanzapine. Eli Lilly and Company, Indianapolis, IN, 2000.

Product Information: Zyprexa(R), olanzapine; Eli Lilly & Co., Indianapolis, IN, 1996. Zyprexa(R), olanzapine; Eli Lilly & Co., Indianapolis, IN, 1996.

Product Information: Zyprexa. Eli Lilly, US, 96.

Product Information: Zyprexa®, olanzapine. Eli Lilly and Company, Indianapolis, IN, 2004.

Quinn NP: Antiparkinsonian drugs today. Drugs 1984; 28:236-262.

Rahman MA & Gregory R: Trichotillomania associated with HIV infection and response to sertraline. Psychosomatics 1995; 36(4):417-418.

Raja M, Altavista MC, & Albanese A: Tardive lingual dystonia treated with clozapine. Mov Disord 1996; 11:585-586.

Ramankutty G: Olanzapine-induced destabilization of diabetes in the absence of weight gain. Acta Psychiatr Scand 2002; 105:235-237.

Ramos RH & Budman CL: Emergence of koro after abrupt cessation of olanzapine (letter). J Clin Psychiatry 1998; 59(2):86-87.

Raskin S, Durst R, Katz G, et al: Olanzapine and sulpiride: a preliminary study of combination/augmentation in patients with treatment-resistant schizophrenia. J Clin Psychopharmacol 2000; 20(5):500-503.

Raskind MA, Cyrus PA, Ruzicka BB, et al: The effects of Metrifonate on the cognitive, behavioral, and functional

performance of Alzheimer's Disease in patients. J Clin Psychiatry 1999; 60:318-325.

Ravindran AV, Lapierre YD, & Anisman H: Obsessive compulsive spectrum disorders: effective treatment with paroxetine. Can J Psychiatry 1999; 44(8):805-807.

Raz A, Bergman R, Eilam O, et al: A case report of olanzapine-induced hypersensitivity syndrome. Am J Med Sci 2001; 321:156-158.

Reilly PP: RI Med J 1977; 60:455-456. RI Med J 1977; 60:455-456.

Reiter S, Adler L, Angrist B, et al: Effects of verapamil on tardive dyskinesia and psychosis in schizophrenic patients. J Clin Psychiatry 1989; 50:26-27.

Risse SC, Lampe TH, & Cubberley L: Very low-dose neuroleptic treatment in two patients with agitation associated with Alzheimer's disease. J Clin Psychiatry 1987; 48:207-208.

Roane DM, Feinberg TE, Meckler L, et al: Treatment of dementia-associated agitation with gabapentin. J Neuropsychiatry Clin Neurosci 2000; 12:40-43.

Robinson RL, Burk MS, & Raman SS: Fever, delirium, autonomic instability, and monocytosis associated with olanzapine (letter). J Postgrad Med 2003; 49:96.

Rochon PA, Stukel TA, Sykora K, et al: Atypical antipsychotics and parkinsonism. Arch Intern Med 2005; 165:1882-1888.

Rudolf J, Ghaemi M, & Schmulling S: Deterioration of parkinsonian symptoms following treatment of dopaminergic hallucinosisi with olanzapine. Eur Psychiatry 1999; 14:356-357.

Safirstein B, Shulman LM, & Weiner WJ: Successful treatment of hemichorea with olanzapine (letter). Mov Disord 1999; 14(3):532-533.

Saleh JW & Lebwohl P: Metoclopramide-induced gastric emptying in patients with anorexia nervosa. Am J Gastroenterol 1980; 74:127-132.

Sanders RD & Mossman D: An open trial of olanzapine in patients with treatment-refractory psychoses. J Clin Psychopharmacol 1999; 19(1):62-66.

Sandyk R & Hurwitz MD: Toxic irreversible encephalopathy induced by lithium carbonate and haloperidol. S Afr Med J 1983; 65:875-876.

Sanger TM, Lieberman JA, Tohen M, et al: Olanzapine versus haloperidol treatment in first-episode psychosis. Am J Psychiatry 1999; 156:79-87.

Santone G, Cotani P, Giuliani S, et al: Tardive dyskinesia remission during risperidone therapy. Clin Drug Invest 1997; 14:502-506.

Schneider LS, Dagerman KS, & Insel P: Risk of death with atypical antipsychotic drug treatment for dementia: Meta-analysis of randomized placebo-controlled trials. JAMA 2005; 292:1934-1943.

Schooler NR: Comments on article by Tran and colleagues, "double-blind comparison of olanzapine versus

risperidone in treatment of schizophrenia and other psychotic disorders" (letter). J Clin Psychopharmacol 1998; 18(2):174-175.

Seaburg HL, McLendon BM, & Doraiswamy PM: Olanzapine-associated severe hyperglycemia, ketonuria, and acidosis: case report and review of literature. Pharmacotherapy 2001; 21(11):1448-1454.

Serra-Mestres J, Shapleske J, & Tym E: Treatment of palilalia with trazodone (letter). Am J Psychiatry 1996; 153:580-581.

Shapira NA, Ward HE, Mandoki M, et al: A double-blind, placebo- controlled trial of olanzapine addition in fluoxetine-refractory obsessive-compulsive disorder. Biol Psychiatry 2004; 55(5):553-555.

Sheldon LJ, Ancill RJ, & Holliday SG: Gabapentin in geriatric psychiatry patients (letter). Can J Psychiatry 1998; 43(4):422-423.

Shelton PS & Brooks VG: Estrogen for dementia-related aggression in elderly men. Ann Pharmacother 1999; 33:808-812.

Shenefelt PD: Hypnosis in Dermatology. Arch Dermatol 2000; 136(3):393-399.

Shi L, Namjoshi MA, Zhang F, et al: Olanzapine versus haloperidol in the treatment of acute mania: clinical outcomes, health-related quality of life and work status. Int Clin Psychopharmacol 2002; 17(5):227-237.

Sierra-Biddle D, Herran A, Diez-Aja S, et al: Neuroleptic malignant syndrome and olanzapine (letter). J Clin Psychopharmacol 2000; 20:704-705.

Silberstein SD, Peres MFP, Hopkins MM, et al: Olanzapine in the treatment of refractory migraine and chronic daily headache. Headache 2002; 42:515-518.

Simon AE, Aubry J-M, Malky L, et al: Hypomania-like syndrome induced by olanzapine. Int Clin Psychopharmacol 1999; 14:377-378.

Simpson GM, Glick ID, Weiden PJ, et al: Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. Am J Psychiatry 2004; 161(10):1837-1847.

Singh HK, Markowitz GD, & Myers G: Esotropia associated with olanzapine (letter). J Clin Psychopharmacol 2000; 20:488.

Sipahimalani A & Masand PS: Olanzapine in the treatment of delirium. Psychosomatics 1998; 39:422-430.

Snyder S: Trichotillomania treated with amitriptyline. J Nerv Ment Dis 1980; 168:505-507.

Soriano JL, O'Sullivan RL, Baer L, et al: Trichotillomania and self-esteem: a survey of 62 female hair pullers. J Clin Psychiatry 1996; 57(2):77-82.

Soutullo CA, Keck PE Jr, & McElroy SL: Olanzapine in the treatment of tardive dyskinesia: a report of two cases (letter). J Clin Psychopharmacol 1999; 19(1):100-101.

Soutullo CA, Keck PE Jr, & McElroy SL: Olanzapine in the treatment of tardive dyskinesia: a report of two

cases (letter). J Clin Psychopharmacol 1999a; 19(1):100.

Spivak B, Mester R, Abesgaus J, et al: Clozapine treatment for neuroleptic-induced tardive dyskinesia, parkinsonism, and chronic akathisia in schizophrenic patients. J Clin Psychiatry 1997; 58:318-322.

Spring GK: Neurotoxicity with the combined use of lithium and thioridazine. J Clin Psychiatry 1979; 40:135-138.

Stacher G, Abatzi-Wenzel T-A, Wiesnagrotzki S, et al: Gastric emptying, body weight, and symptoms in primary anorexia nervosa: long-term effects of cisapride. Br J Psychiatry 1993; 162:398-402.

Stamenkovic M, Schindler SD, Aschauer HN, et al: Effective open-label treatment of Tourette's disorder with olanzapine. Int Clin Psychopharmacol 2000; 15:23-28.

Stanfield SC & Privette T: Neuroleptic malignant syndrome associated with olanzapine therapy: a case report. J Emerg Med 2000; 19:355-357.

Stein DJ & Hollander E: Low-dose pimozide augmentation of serotonin reuptake blockers in the treatment of trichotillomania. J Clin Psychiatry 1992; 53(4):123-126.

Stein DJ, Bouwer C, & Maud CM: Use of the selective serotonin reuptake inhibitor citalopram in treatment of trichotillomania. Eur Arch Psychiatry Clin Neurosci 1997; 247(4):234-236.

Stein DJ, Simeon D, Cohen LJ, et al: Trichotillomania and obsessive-compulsive disorder. J Clin Psychiatry 1995; 56 (suppl 4):28-34.

Stein GS: Lithium in a case of severe anorexia nervosa. Br J Psychiatry 1982; 140:526-528.

Stein MB, Kline NA, & Matloff JL: Adjunctive olanzapine for SSRI- resistant combat-related PTSD: a double-blind, placebo-controlled study. Am J Psychiatry 2002; 159(10):1777-1779.

Stemberger RM, Thomas AM, Mansueto CS, et al: Personal toll of trichotillomania: behavioral and interpersonal sequelae. J Anxiety Disord 2000; 14(1):97-104.

Stevenson RN, Blanshard C, & Patterson DLH: Ventricular fibrillation due to lithium withdrawal - an interaction with chlorpromazine?. Postgrad Med J 1989; 65:936-938.

Stewart RS & Nejtek VA: An open-label, flexible-dose study of olanzapine in the treatment of trichotillomania. J Clin Psychiatry 2003; 64(1):49-52.

Straker D, Mendelowitz A, Karlin L, et al: Near fatal ketoacidosis with olanzapine treatment (letter). Psychosomatics 2002; 43(4):339-340.

Strauss AJL, Bailey RK, Dralle PW, et al: Conventional psychotropic-induced tremor extinguished by olanzapine (letter). Am J Psychiatry 1998; 155:1132.

Street JS, Clark WS, Gannon KS, et al: Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzeheimer disease in nursing care facilitites. Arch Gen Psychiatry 2000; 57:968-976.

Street JS, Clark WS, Kadam DL, et al: Long-term efficacy of olanzapine in the control of psychotic and behavioral symptoms in nursing home patients with Alzheimer's dementia. Int J Geriatr Psychiatry 2001; 16:S62-S70.

Swedo SE, Leonard HL, Rapoport JL, et al: A double-blind comparison of clomipramine and desipramine in the treatment of trichotillomania (hair pulling). N Engl J Med 1989; 321:497-501.

Tariot PN, Erb R, Podgorski CA, et al: Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. Am J Psychiatry 1998; 155:54-61.

Tariot PN: Treatment of agitation in dementia. J Clin Psychiatry 1999; 60(suppl):11-20.

Teter CJ, Early JJ, & Frachtling RJ: Olanzapine-induced neutropenia in patients with history of clozapine treatment:two case reports from a state psychiatric institution. J Clin Psychiatry 2000; 61(11):872-873.

Thomas CJ: Brain damage with lithium/haloperidol (letter). Br J Psychiatry 1979; 134:552.

Thomas SG & Labbate LA: Management of treatment-resistant schizophrenia with olanzapine (letter). Can J Psychiatry 1998; 43(2):195-196.

Tohen M, Baker RW, Altshuler LL, et al: Olanzapine versus divalproex in the treatment of acute mania. Am J Psychiatry 2002; 159(6):1011-1017.

Tohen M, Chengappa KNR, Suppes T, et al: Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. Arch Gen Psychiatry 2002a; 59:62-69.

Tohen M, Jacobs TG, Grundy SL, et al: Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. Arch Gen Psychiatry 2000; 57(Sep):841-849.

Tohen M, Sanger TM, McElroy SL, et al: Olanzapine versus placebo in the treatment of acute mania. Am J Psychiatry 1999; 156:702-709.

Tohen M, Vieta E, Calabrese J, et al: Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry 2003; 60(11):1079-1088.

Tollefson DG, Sanger TM, & Thieme ME: Depressive signs and symptoms in schizophrenia: a prospective blinded trial of olanzapine and haloperidol. Arch Gen Psychiatry 1998a; 55:250-258.

Tollefson GD & Kuntz AJ: Review of recent clinical studies with olanzapine. Br J Psychiatr 1999; 174(suppl 37):30-35.

Tollefson GD, Beasley CM Jr, Tran PV, et al: Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Paychiatry 1997a; 154:457-465.

Tollefson GD, Beasley CM Jr, Tran PV, et al: Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Paychiatry 1997b; 154:457-465.

Tollefson GD, Beasley CM Jr, Tran PV, et al: Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Psychiatry 1997; 154:457-465.

Tollefson GD, Beasley CM, Tran PV, et al: Olanzapine: a novel antipsychotic with a broad spectrum profile (abstract 477). Biol Psychiatry 1994; 35:615-747.

Tollefson GD, Sanger TM, Lu Y, et al: Depressive signs and symptoms in schizophrenia. Arch Gen Psych 1998; 55:250-258.

Tolosa-Vilella C, Ruiz-Ripoll, Mari-Alfonso B, et al: Olanzapine-induced agranulocytois. A case report and review of the literature. Neuropharmacology 2002; 26:411-414.

Toren P, Laor N, & Weizman A: Use of atypical neutoleptics in child and adolescent psychiatry. J Clin Psychiatry 1998; 59:644-656.

Tran PV, Dellva MA, Tollefson GD, et al: Extrapyramidal symptoms and tolerability of olanzapine versus haloperidol in the acute treatment of schizophrenia. J Clin Psychiatry 1997; 58:205-211.

Tran PV, Hamilton SH, Kuntz AJ, et al: Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. J Clin Psychopharmacol 1997a; 17:407-418.

Trosch RM, Friedman JH, Lannon MC, et al: Clozapine use in Parkinson's disease: a retrospective analysis of a large multicentered clinical experience. Mov Disord 1998; 13(3):377-382.

Van Ameringen M, Mancini C, Oakman JM, et al: The potential role of haloperidol in the treatment of trichotillomania. J Affect Disord 1999; 56(2-3):219-226.

Verma SD, Davidoff DA, & Kambhampati KK: Management of the agitated elderly patient in the nursing home: the role of the atypical antipsychotics. J Clin Psychiatry 1998; 59(suppl 19):50-55.

Vernon LT, Fuller MA, Hattab H, et al: Olanzapine-induced urinary incontinence: treatment with ephedrine. J Clin Psychiatry 2000; 61:601-602.

Vieta E, Reinares M, Corbella B, et al: Olanzapine as long-term adjunctive therapy in treatment-resistant bipolar disorder. J Clin Psychopharmacol 2001; 21(5):469-473.

Vigersky RA & Loriaux DL: The effect of cyproheptadine in anorexia nervosa: A double blind trial. In: Vigersky RA (Ed). Anorexia Nervosa, Raven Press, New York, NY; pp 349-356, 1977.

Volavka J, O'Donnell J, Muragali R, et al: Lithium and lecithin in tardive dyskinesia: an update. Psychiatry Res 1986; 19:101-104.

Waage IM & Gedde-Dahl A: Pulmonary embolism possibly associated with olanzapine treatment. BMJ 2003; 327(7428):1384.

Wadlington WB, Rose M, & Holcomb GW: Complications of trichobezoars: a 30-year experience. South Med J 1992; 85(10):1020-1022.

Walker Z, Grace J, Satarasinghe S, et al: Olanzapine in dementia with lewy bodies: a clinical study. Int J Geriatr Psychiatry 1999; 14:459-466.

Wang PS, Schneeweiss S, Avorn J, et al: Risk of death in elderly users of conventional vs. atypical antipsychotic

medications. N Engl J Med 2005; 353:2335-2341.

Weller EB, Weller RA, & Carr S: Imipramine treatment of trichotillomania and coexisting depression in a seven-year-old. J AmAcad Child Adolesc Psychiatry 1989; 6:952-953.

White JA & Schnaultz NL: Successful treatment of anorexia nervosa with imipramine. Dis Nerv Syst 1977; 38:567-568.

Wijkstra J, Lijmer J, Balk F, et al: Pharmacological treatment for psychotic depression. Cochrane Database Syst Rev 2005; (4):CD004044.

Wolters EC, Jansen ENH, Tuynman-Qua HG, et al: Olanzapine in the treatment of dopaminomimetic psychosis in patients with Parkinson's disease. Neurology 1996; 47:1085-1087.

Wolters EC, Jansen ENH, Tuynman-Qua HG, et al: Olanzapine in the treatment of dopaminomimetic psychosis in patients with Parkinson's disease. Neurology 1996a; 47:1085-1087.

Woodall BS & DiGregorio RV: Comment: olanzapine-induced acute pancreatitis. Ann Pharmacother 2001; 35:506-507.

Woods SW, Breier A, Zipursky RB, et al: Randomized trial of olanzapine versus placebo in the symptomatic acute treatment of the schizophrenic prodrome. Biol Psychiatry 2003; 54(4):453-464.

Wyderski RJ, Starrett WG, & Abou-Saif A: Fatal status epilepticus associated with olanzapine therapy. Ann Pharmacother 1999; 33:787-789.

Yanchick JK, Barton TL, & Kelly MW: Efficacy of Fluoxetine in Trichotillomania. Ann Pharmacother 1994; 28:1245-1246.

Yetimalar Y, Irtman G, Gurgor N, et al: Olanzapine efficacy in the treatment of essential tremor. Eur J Neurol 2003; 10:79-82.

Yip L & Graham K: Clinical effects of olanzapine in a 2 1/2-year-old male. J Toxicol Clin Toxicol 1997; 35:1997.

Zall H, Therman PG, & Myers JM: Lithium carbonate: a clinical study. Am J Psychiatry 1968; 125:549-555.

Zanarini MC & Frankenburg FR: Olanzapine treatment of female borderline personality disorder patients: a double-blind, placebo-controlled pilot study. J Clin Psychiatry 2001; 62:849-854.

Zarate CA, Narendran R, Tohen M, et al: Clinical predictors of acute response with olanzapine in psychotic mood disorders. J Clin Psychiatry 1998; 59(1):24-28.

Zarate CA: Antipsychotic drug side effect issues in bipolar manic patients. J Clin Psychiatry 2000; 61(8):52-61.

Zyprexa package insert (Eli Lilly—US). Rev Rec 10/96., 9/96.

de Jong J, Hoogenboom B, van Troostwijk L, et al: Interaction of olanzapine with fluvoxamine. Psychopharmacology 2001; 155:219-220.

DRUGDEX-EV 1728

END OF DOCUMENT